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**A Qualitative Study of Cystic Fibrosis (CF) Patients'
Expectations of Gene Therapy**

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ABSTRACT

Introduction: Gene therapy is currently being developed for people with cystic fibrosis (CF), a life-threatening condition for which there is no cure. The UK CF Gene Therapy Consortium are preparing for a multi-dose gene therapy trial of sufficient duration that clinical benefit may be seen.

Aims: The current study aimed to explore the expectations and beliefs of cystic fibrosis (CF) patients involved in the preparatory phase of the gene therapy trial (the Run-in study), from which participants will be selected for the multi-dose actual gene therapy trial.

Method: Twelve participants (six with mild and six with moderate CF) were interviewed using a semi-structured interview. Interviews were recorded, transcribed verbatim and then analysed using a Constructivist Grounded Theory approach.

Results: Since entering the Run-in study, half of the patients had increased their expectations of gene therapy being an effective future treatment. Most of the participants hoped to derive clinical benefit from the trial itself though half were unsure of what to expect. Whilst half of the participants expressed the hope of a future cure for CF, the remainder saw gene therapy only in terms of an improved treatment. Participants used several strategies to manage their expectations including not thinking too far ahead and trusting the research team.

Discussion: The findings indicate that participants in the Run-in trial are generally eager to be involved in the gene therapy trial and have developed a strong sense of trust in the research team conducting the trials. The levels of optimism expressed for personal benefit from trial were higher than those from earlier studies. Some of the positive expectations were unlikely to be met by the gene therapy trial and participants risk disappointment. However other patients participated with apparently realistic expectations and it seems likely that some patients would have participated even without prospect for personal benefit. Possible areas of psychological support are discussed e.g. a standard clinical interview for all those not accepted for the gene therapy trial; screening for anxiety pre-, during and post-participation.

1 Introduction

1.1 Overview of CF (CF)

Cystic fibrosis (CF) is the most common life-threatening recessive genetic disease in the UK. It arises due to mutations in the protein of the CF gene i.e. the CF transmembrane conductance regulator (CFTR). CF has an incidence of 1 in every 2381 live births in the UK (Dodge *et al.*, 2007) and currently affects more than 8,000 people. Approximately 1 person in 25 in the UK population carries the faulty gene that causes CF. There is as yet no known cure for CF. Treatment is palliative and health is maintained by treating disease symptoms as they arise (Lowton, 2005). Symptoms include bronchopulmonary infections, pancreatic insufficiency and CF related diabetes. Treatment involves a range of daily therapies underpinned by chest physiotherapy, antibiotics for chest infections and pancreatic enzymes to facilitate food absorption and encourage a healthy weight (Morton *et al.*, 2006). Bronchopulmonary infections result in progressive lung damage and respiratory disease is the biggest cause of death in the CF population (Griesenbach *et al.*, 2006; Parsons, 2005; Wagner & Gardner, 1997).

1.2 Prevalence of CF

CF is the most common life-threatening genetic disease in the Caucasian population (Bossi *et al.*, 2004). There is an estimated birth prevalence in Scotland of one in 1500, taking into account both dominant and mild forms of CF (Brock *et al.*, 1998). However, there is some variation in the prevalence rates reported. Welsh *et al.* (1995) state that the usual prevalence of CF is 1 in every 2,000 to 3,000 live births in populations of European descent.

Estimating the birth prevalence of CF is complicated due to the range of severity caused by specific heterozygotes (Brock *et al.*, 1998). There is evidence to suggest that incidence values vary within distinct geographic areas from 1 in 1,800 to 1 in 8,500 and that there is therefore specificity of prevalence for populations (Bossi *et al.*, 2004). Although CF affects all races and ethnic groups, the prevalence of CF in Asiatic and other non-Caucasian ethnic groups remains extremely low, with one example being the incidence of around 1 in 350,000 in the Japanese population (Yamashiro *et al.*, 1997).

1.3 Diagnosis

1.3.1 Time of Diagnosis

Since the early nineteen-seventies, newborn screening protocols for CF have gradually developed and are now being implemented in 26 countries including the UK (Castellani *et al.*, 2009). Diagnosis for CF is now routinely made in infancy. This is by means of a heel-prick to sample blood. The sweat test is also used to detect the high level of salt in the sweat of people with CF. Prior to this, diagnosis was made based on tests that included a sweat test in babies and children who were failing to thrive.

However, there have been differences in screening practice and data collection criteria between countries (Farrell, 2008). Although there is no possibility of a single European screening approach due to factors such as variations in healthcare resources and ethnic mix of populations, the benefit of screening protocols is that more than 3,000,000 babies are being screened in Europe each year (Castellani *et al.*, 2009). This wider use of neonatal screening has improved CF diagnosis in babies (e.g. Bossi *et al.*, 2004).

In a comparative analysis of CF Registry data from 2001 from the UK, France, Australasia and the USA, the rate of diagnosis of children with CF was 70% in the UK and the USA populations respectively compared to 73% in France and 94.3% in Australasia (McCormick *et al.*, 2005). Full national neonatal screening was not being undertaken in the UK at this stage. By 2007, 33.1% of all recorded diagnoses made were at 0 to 3 months compared to later diagnosis i.e. 2.1% of 21 to 30 year olds and 1.4% of 31 to 40 years olds. The median age of diagnosis was 5 months which illustrates that with the introduction of neonatal screening the age of diagnosis of CF had fallen considerably which bodes well for treatment.

1.3.2 Late Diagnosis

When screening is absent there may be a delay in diagnosis, particularly if the clinical presentation is uncertain (Wideman *et al.*, 2000). Diagnosis may not occur until adulthood amongst those who present with mild or atypical forms of CF (Wideman *et al.*, 2000). In a study comparing one group of 27 late diagnosis CF patients (median age of 48.8 years at diagnosis) to a group of 28 early diagnosis patients (median age at diagnosis was 2 years), those with a late diagnosis had less prevalence of CF related diabetes, normal pancreatic function, better nutritional status and milder lung disease (Rodman *et al.*, 2005). Just one patient in the late diagnosis group was $\Delta F508$ homozygous, which is the most common and most potentially severe mutation (McAuley & Elborn, 2000, Rana-Diez *et al.*, 2008), compared with ten patients in the early diagnosis category. The late diagnosis group displayed a higher prevalence of milder class or unidentified mutations overall (Rodman *et al.*, 2005). However, those who are diagnosed late have specific areas in which they require support as they adjust

to their diagnosis e.g. relationships, family planning and work-related decisions (Widerman, 2003).

1.4 Mutations

In 1989, the CF gene was identified on chromosome 7 (e.g. Bossi *et al.*, 2004). The gene encodes protein to make a chloride channel in the apical membrane of the epithelial cells (e.g. Griesenbach *et al.*, 2004a). Currently over 1400 different mutations within the gene have been identified (Rana-Diez *et al.*, 2008). However, only a minority of mutations have been confirmed as causing disease (Welsh & Smith, 1993).

CF occurs when a person inherits an abnormal copy of the CF gene from each parent and neither copy of the gene can produce functional CFTR protein (e.g. Bossi *et al.*, 2004, Gozdzik *et al.*, 2005). The most common mutation is delta F508 ($\Delta F508$) which makes copies of the CFTR protein without phenylalanine, an amino acid usually found in position 508 (Riordan *et al.*, 1989). Homozygous patients with $\Delta F508/\Delta F508$ demonstrate significantly reduced levels of CFTR function and are associated with greater disease severity i.e. CF lung disease, obstructive azoospermia and pancreatic insufficiency (McAuley & Elborn, 2000). For heterozygous patients with one copy of $\Delta F508$, a different mutation affects their second copy of the CF gene (MacDonald *et al.*, 2007). There is variation in clinical expression of mutations since the second mutation may be akin to $\Delta F508$ in eliminating almost all CFTR function or it may have a lesser effect (MacDonald *et al.*, 2007). It is estimated that around 90% of people with CF have at least one copy of $\Delta F508$ (MacDonald *et al.*, 2007).

The distribution of mutations appears to be specific to race and/or ethnic origin (Collazo *et al.*, 2009), with the dominant $\Delta F508/\Delta F508$ homozygous mutation

accounting for 27% of the Italian CF population compared to at least 50% in Northern Europe and the United States (Bossi *et al.*, 2004). There is no evidence of the $\Delta F508$ mutation in the Japanese CF population (Yamashiro *et al.*, 1997). There are associations between mutations and disease severity (Rana-Diez *et al.*, 2008) yet generally the CF genotype-phenotype association is not recognised as being strong, albeit genotype may predict pancreatic status (Mackie *et al.*, 2003). For example, it has been suggested that the rare genotype N1303K increases the risk of diabetes (Cotellessa *et al.*, 1996), but this association has not been verified in other studies (Mackie *et al.*, 2003).

In addition, there is growing evidence that several variants in other genes modify the clinical course of CF lung disease i.e. those influencing infection, immunity and inflammation control (Buscher & Grasemann, 2006). For example, the TNFAIP gene which is involved in inflammation control was associated with better lung function in one European sample of 180 children with CF who were $\Delta F508$ homozygous (Buscher & Grasemann, 2006).

1.5 Symptoms

CF-causing mutations result in loss of function in the transport system of water and salt in and out of epithelial cells found in the lining of the lungs, the urogenital tract, the sweat glands, and the digestive system (e.g. Brock *et al.*, 1998; Wagner & Gardner, 1997). Typically the CFTR protein in CF patients transports too much salt and not enough water, resulting in sticky mucus which coats and clogs the lungs and alimentary tracts (e.g. Boyd *et al.*, 2004; Griesenbach *et al.*, 2004a).

1.5.1 Lung Disease

Because the lungs of CF patients do not have a functional mucociliary clearance process, whereby particulates like airborne bacteria and viruses are removed from the lungs, there is susceptibility to chronic bacterial infection (Wagner & Gardner, 1997; Mueller & Flotte, 2008). Infection leads to inflammation which in turn leads to mucus plugging, subsequent obstruction and progressive lung damage (e.g. Wagner & Gardner, 1997). Respiratory function subsequently becomes increasingly reduced and resting energy expenditure (REE) is raised (Wilson & Pencharz, 1998). Symptoms include high blood pressure in the lungs, coughing up blood and structural changes in major airways. Like adult patients with other forms of severe chronic lung disease (e.g. chronic obstructive pulmonary disease), most CF patients will die a premature death because of an exacerbation of pulmonary symptoms (Robinson, 2000).

1.5.2 Pancreatic, Gastrointestinal and Liver Disease

Pancreatic abnormalities are present in 85% to 90% of all CF patients (Lugo-Oliveiri *et al.*, 1998). Under-nutrition occurs because of pancreatic insufficiency leading to malabsorption of food since the pancreas no longer produces enzymes required to digest nutrients (Connett, 2006). Poor absorption of vitamin D can lead to osteoporosis. Wilson & Pencharz (1998) highlight that chronic undernutrition, low body weight and linear growth failure are recognised difficulties for patients with CF. Thickened secretions may result in liver problems with bile ducts becoming blocked, leading to the liver not removing toxins from the blood e.g. cirrhosis.

1.5.3 Endocrine Disease

Another complication of CF is CF related diabetes (CFRD) which typically develops at around age 20 (Mackie *et al.*, 2003). This is due to loss of the insulin producing islet cells in the pancreas. CFRD has similarities to Type 1 and Type 2 diabetes and it is recognised as one of the main non-pulmonary complications of CF and a contributory factor in premature death.

1.5.4 Other Symptoms

For men with CF, there is almost universal azoospermic infertility due to congenital bilateral absence of the vasa deferentia (Mackie *et al.*, 2003), with 98% of men with CF requiring assisted conception or donor sperm for conception (Boyd *et al.*, 2004). For women, however, the chances of pregnancy are good and even better when a patient has good respiratory health (Boyd *et al.*, 2004). Further complications include osteoporosis and pancreatitis. Whilst there is no primary renal disease, side-effects from medications such as aminoglycoside antibiotic therapy can adversely affect renal function and may be a contributory factor for peripheral neuropathy (Mackie *et al.*, 2003).

1.6 Current Treatment

Treatment focuses on preventing deterioration of the lungs through the use of physiotherapy, antibiotics and improved nutrition. A multi-disciplinary approach is utilised with the level of intervention dependent upon disease severity. Typically, physiotherapy is used to help keep the patient's airways clear. The use of antibiotics reduces colonisation by bacteria and anti-inflammatory drugs are used to minimise tissue damage. Because of malabsorption, pancreatic enzymes and fat-soluble vitamins

are used respectively to aid digestion and raise vitamin levels to as near normal as possible (e.g. Morton *et al.*, 2006). To help with weight gain, high calorie and high protein food are taken and CF patients are encouraged to eat 120 to 150% of the daily allowance recommended for normal individuals (Wilson & Pencharz, 1998). When appropriate, overnight feeding is used to encourage weight gain. There is growing recognition that effective interventions are required for CF related diabetes and osteoporosis (Dobbin & Bye, 2003). However, there is also growing expectation that increased knowledge of the molecular biology of CF mutations will lead to improved treatments e.g. repairing the CFTR protein function, thereby reducing illness, improving quality of life and increasing life expectancy (MacDonald *et al.*, 2007).

1.7 End-stage Disease

When a person with CF has end-stage lung disease (i.e. lung function that is less than 30% of function predicted for someone of the same age, gender, weight and height), bilateral lung transplantation becomes the most viable therapeutic option for prolonged survival (Meachery *et al.*, 2008). This is in spite of strict acceptance criteria for transplantation (e.g. Schidlow, 2000), and a shortage of donor lungs. Despite potential complications including risk of infection and organ rejection (Studer *et al.*, 2004; Taylor *et al.*, 2008), survival rates in the UK have increased, being 82% at one year, 70% at three years and 51% at ten years (Meachery *et al.*, 2008).

1.8 Life Expectancy

Before 1960, the average life expectancy for CF patients was under five years of age (Wagner & Gardner, 1997). Improved treatment has had a positive impact upon life expectancy and children with CF are increasingly surviving into adulthood (Dobbin &

Bye, 2003). Outcomes for patients with CF now vary from early death due to lung disease through to a normal life span, though the latter is rare (NIH, 1997). In the U.K. the most recent median predicted age of survival is 35.2 years (UK CF Registry, 2007). This compares with 36.4 years in France and 37.4 years in Germany and the U.S. (Buzzetti *et al.*, in press). However, accurate comparison with other data sets is problematical due to differing methods of acquiring information on CF populations (Dodge *et al.*, 2007). For all UK CF patients, the median life expectancy is more likely to be 50 years for those born in 2000 (Dodge *et al.*, 2007). There is also evidence to suggest that the condition of patients at the time of diagnosis strongly influences prognosis (Lai *et al.*, 2004).

1.9 Psychological Impact of Having CF

Despite advances in treatment, CF is still associated with psychological adversities for the patient (Casier *et al.*, 2008). There have been many studies to assess the prevalence of depression and anxiety in the CF population with conflicting evidence about whether there is an association between having CF and psychological functioning (Pfeffer *et al.*, 2003). In some studies, adult CF patients show psychological functioning that is similar to that of physically healthy controls (e.g. Anderson *et al.*, 2001; Blair *et al.*, 1994). In one study young adults with CF seem less prone to developing mental health difficulties than their physically healthy peers (Szyndler *et al.*, 2005). One of the reasons for the discrepancies in these studies may be the fact that older studies are rapidly becoming invalid due to the fact that life expectancy has changed so significantly in the past forty years. This has brought about by changes in the treatment and management of CF (Pfeffer *et al.*, 2003).

The current consensus points to people with CF as falling within the normal population distribution regarding psychological functioning until a point where disease severity becomes significant (Pfeffer *et al.*, 2003; Riekert *et al.*, 2007; Sawicki *et al.*, 2008; Szyndler *et al.*, 2005). There is also the consensus that people with CF may have to deal with certain disease specific issues that may need or benefit from psychological support (Anderson *et al.*, 2001).

Living with Uncertainty

It has been suggested that being able to live with the unpredictable and uncontrollable nature of CF requires the ability to tolerate uncertainty (Casier *et al.*, 2008). This applies to specific issues e.g. predicting whether current lung infection will prove to have fatal consequences (Robinson, 2000) or waiting for a lung transplant (Limbos *et al.*, 2000; Vermeulen *et al.*, 2005) as well as more general issues such as coping with the life-limiting nature of CF.

Some studies have shown that having to tolerate uncertainty can produce anxiety and depression in people with CF (e.g. Havermans *et al.*, 2008) although not all studies have reported this outcome (e.g. Pearson *et al.*, 1991; Pfeffer *et al.*, 2003). These findings point to the fact that all people with CF have to tolerate a variety of forms of uncertainty, with some finding this more difficult than others. Indeed in a study of lung transplant recipients it was found that strategies employed to manage uncertainty, namely focusing on the present, resulted in participants experiencing a stronger sense of self in the post transplant period (Durst, 2001).

Quality of Life

As most people with CF are now surviving into adulthood, the issue of quality of life becomes an important issue in the absence of a cure for CF. A number of studies have investigated this. As above, these studies have highlighted that there was little difference in quality of life between healthy controls and CF patients until disease severity increased (Pfeffer *et al.*, 2003; Sawicki *et al.*, 2008; Wahl *et al.*, 2005). However, it is accepted that people with CF also have to manage the demanding regimen of intensive daily treatments (Casier *et al.*, 2008).

Depressive symptoms are also associated with poorer quality of life and this indicates that screening for depression and appropriate treatment may improve health-related quality of life for patients with CF (Riekert *et al.*, 2007). Wahl *et al.* (2005) suggest that further research is needed to gain knowledge of the effect on quality of life of living longer with CF and on how to promote quality of life for those living with a life-threatening disease.

Role of Psychologist

A specialist clinical psychologist can help adults with CF to find the best personal way to cope with CF (Oxley & Webb, 2005). This involves not only addressing psychological needs that may be specific to an individual or their stage of disease, but may also involve screening for anxiety and depression. This is important as anxiety and depression have been recognised in other long-term conditions as risk factors for increased use of the health care system, poor adherence to treatment and increased mortality. Havermans *et al.* (2008) suggest that anxiety and depression screening could be used to target areas of clinical need and thereby prevent these risk factors. Indeed,

the CF Trust recommend that all CF centres have access to a specialist CF clinical psychologist who co-ordinates routine screening of anxiety and depression as well as administering a validated quality of life measure as part of ongoing annual review tests (CF Trust, 2001).

1.10 Gene Therapy

Gene therapy research is currently taking place into its application to over twenty diseases (Meneguzzi *et al.*, 2007). Researchers have observed that no one specific gene transfer agent (GTA) is suitable for all genetic diseases, but that disease-specific gene therapy is required (Griesenbach & Alton, 2009). Researchers have acknowledged the need for further study of the immune response to GTAs, but following the unfortunate death in 1999 of an 18 year old male patient participating in a non-CF pilot trial of gene transfer, they have proceeded with caution (Raper *et al.*, 2003).

Gene Therapy for CF

Since the discovery and subsequent cloning of the CF transmembrane conductance regulator (CFTR) gene in 1989, CF has been an attractive target for gene therapy research (Mueller & Flotte, 2008). Early enthusiasm for the novel area of gene therapy in the 1990s led to a concerted effort by academics and clinicians to apply CF gene therapy (Mueller & Flotte, 2008). It was felt that “considerable progress” had been made (Middleton & Alton, 1998, p.197). The CF Trust currently spends just over 75% of its annual budget to research in gene therapy, with the remainder being spent on research into other features such as drug therapy and inflammation (CF Trust, 2009). However, gene transfer therapy is significantly more complex than was first understood

and to date, there are no approved therapies targeted at the CFTR protein (Pearson, 2009).

CF Gene Therapy Studies to Date

A review of relevant empirical studies provides the context and the rationale for the present qualitative study.

As a disease with a single gene defect, CF is likely to be targeted more efficiently than diseases involving multiple genetic locations (Griesenbach & Alton, 2009). Most research is focused on the respiratory system due to the greatest pathophysiology being within the lung (e.g. Wagner & Gardner, 1997). Since 1989, 25 phase I and II clinical trials have been undertaken, with most of the early trials targeting nasal epithelium as a lung surrogate in order to test access and sampling (Griesenbach & Alton, 2009). The trials in the early 1990s served to establish proof-of-principle for the gene transfer to the epithelial lining cells of the lungs (Griesenbach *et al.*, 2004b). There is also evidence of partial correction of chloride transport in several clinical studies undertaken (Griesenbach & Alton, 2009). One such trial involved the gene transfer agent (GL67) being administered to the lungs for the first time (Alton *et al.*, 1999). These early studies provided further support for the possibility of gene therapy for patients with CF (Griesenbach *et al.*, 2006).

Requirements of effective gene therapy for CF

Effective gene therapy treatment for CF airway disease requires the development of gene transfer agents that can penetrate the airway epithelial cells' defence mechanisms against foreign bodies (e.g. Boucher, 1999; Koehler *et al.*, 2001). Set within the reality of the lungs being routinely infected by pathogens, it is theoretically possible to

develop gene therapy treatment that can cross the lung's defences (Koehler *et al.*, 2001). However, this defence response has been underestimated, engendering the need for improved knowledge of host cells' interaction (Griesenbach & Alton, 2009). An efficient transfer agent is needed to maximise gene transfer whilst being able to minimise hostile immune responses to the agent and to be able to deliver repeat administrations of gene therapy (Koehler *et al.*, 2001).

New strategies are being developed to improve the efficiency of gene therapy delivery and the length of time the gene remains in the lung (Griesenbach & Alton, 2009). Clinical trials of sufficient duration with adequately powered sample sizes are required, as is repeated administration of a gene therapy agent to correct the defective gene (Griesenbach *et al.*, 2006; Griesenbach & Alton, 2009). Clinical studies require clear endpoints and outcome measures that are specific to people with CF (Lee & Southern, 2009). Griesenbach & Boyd. (2005) suggest the most important endpoint in later trials is stabilisation of lung function, albeit this may be somewhat difficult to measure as those with good function will be the most likely to respond successfully to gene therapy. Griesenbach & Boyd (2005) also suggest the use of a validated quality of life questionnaire to elicit feelings and opinions of patients in order to gain valuable information about the progress of gene therapy trials. A further factor is patient selection since CF gradually damages the airways and gene therapy may prevent or reduce further damage but will not repair damage. As such, gene therapy "will likely be most efficient and beneficial in young children with well preserved airways" although biomarkers may be harder to identify in their relatively unaffected lungs (Griesenbach & Alton, 2009, p.134).

CF has been genetically replicated in mice (e.g. Hilliard *et al.*, 2008) and in pigs (Rogers *et al.*, 2008) with the aim of understanding how CF develops e.g. whether infection precedes airway inflammation or vice versa. Whilst both animal models have provided data regarding CF, mice do not develop the lung disease found in humans and it is still not clear how lung disease will develop in pigs (Rogers *et al.*, 2008). It is therefore premature to use animal models in gene therapy trials that target the lung. Consequently, human trials are required to be undertaken with consenting participants.

CF Run-in Study

The UK CF Gene Therapy Consortium designed the Run-in study as the pre-treatment selection phase for participants and for establishing baseline measurements for a subsequent gene therapy trial (See below). Participants on the Run-in study are aged ten upwards but because of ethical considerations, the current study was restricted to adults i.e. aged sixteen and older.

The Run-in study will develop understanding of how CF changes over time, thereby helping researchers to select the best methods of measuring changes in the lung in the gene therapy trial. Criteria for patient selection will also be developed. The Run-in study started in February 2008 and participants' entry onto this has been staggered. Participants in the Run-in study attend four visits over a one-year period and each visit lasts for approximately three hours. During the study visit, participants are asked to undertake a series of tests to measure lung function. Those who have participated in the Run-in study will be considered for selection to the gene therapy trial currently scheduled for 2011.

Gene Therapy Trial

Preparations are now being made for the multi-dose gene therapy trial, which will be placebo-controlled and double-blinded (Griesenbach & Alton, 2009). It is expected to be the biggest gene therapy trial undertaken to date for CF (Pearson, 2009). The purpose of the trial is to assess whether the non-viral gene therapy agent Genzyme lipid 67 (GL67) can be delivered safely to the lungs over a period of time and whether it improves clinically appropriate endpoints like infection, inflammation and lung function (Griesenbach & Alton, 2009). A single dose pilot is being used to assess the safety and length of gene expression in the lungs before the multi-dose GL67/DNA complexes are administered over a twelve-month period. It is anticipated that there will be approximately fifty participants in the active treatment group and fifty participants receiving the placebo.

Based on rational scientific principles, it is also anticipated that the treatment is likely to work best in those with early disease and therefore particularly well in children (Griesenbach & Alton, 2009; J.A.Innes, personal communication, 24 June 2009). It would be harder to correct the gene in those with advanced CF because of more severe lung disease i.e. secondary chronic bacterial infection and associated scarring of the lung membrane. However, the magnitude of any clinical benefit from the trial is as yet unknown and the trial is designed to allow investigators to look for changes that indicate clinical benefit (J.A.Innes, personal communication, 24 June 2009).

The Research Community's Expectations of CF Gene Therapy Trials

In a paper on the status of gene therapy for CF, Richard Boucher wrote in 1999:

“ Despite an impressive amount of research in this area, there is little

evidence to suggest that an effective gene-transfer approach for the treatment of CF lung disease is imminent (p.441).”

Because developing CF gene therapy has taken longer and has been more complex than anticipated, there has been a reduction in academic and industrial interest in CF gene therapy over the past ten years (Griesenbach & Alton, 2009). Although progress within gene therapy for CF has taken longer than anticipated, and indeed has been described as slow, CF is not alone since this is representative of the field of gene therapy generally (Parsons, 2005). In terms of development, one approach is to compare its progress to the development of other medical advances such as vaccines or antibiotics. Within this context, the development of a successful medical technology is expected to take longer than that of a drug developed within an established therapeutic system (Parsons, 2005).

It is recognised that the progress of clinical trials does not initially match advances in preclinical research (Griesenbach *et al.*, 2004b). Rapid progress in CF gene therapy was initially anticipated due to proof in principle of non-invasive access to lung epithelial cells, but this still presents a challenge in practice (Griesenbach *et al.*, 2004b). Whilst there have been no dramatic clinical benefits to date, the gene therapy pre-clinical and clinical studies have provided significant information that has informed gene transfer technology and has helped with understanding the defence mechanisms that impede efficient delivery (Mueller & Flotte, 2008). The potential benefits of successful delivery of gene therapy are motivating factors in overcoming the current barriers.

Expectations of Gene Therapy within the CF Population

As difficulties in developing gene therapy have been encountered since 1989, hopes of the potential of this treatment have fluctuated in CF patients and their families. There is

some evidence for CF patients having more awareness of gene therapy compared to the wider population (Iredale *et al.*, 2003). The media has been shown to influence participant knowledge regarding experimental gene therapy (Blair *et al.*, 1998) and participants in trials and the general public are susceptible to misinterpreting preliminary data and thereby to developing unrealistic hopes and expectations (Skach, 2002).

Writing ten years ago, Dodge (1998) was of the opinion that people with CF had unrealistic hopes of the potential of gene therapy. Dodge (1998) posited that the “delivery of gene therapy cannot be guaranteed” (p.158), therefore emphasis should be placed upon improving existing treatments and developing new pharmacological approaches. Patients with CF have benefited from clinical advances and this, as well as knowledge of research currently being undertaken into new treatments, has led to increased hope and expectation of effective treatment for CF (Dobbin & Bye, 2003). There is, however, increasing confidence in gene therapy becoming a safe and successful treatment (Davies *et al.*, 2001; CF Today 2005/2006). In a study considering the ethics of children participating in children’s gene therapy trials (Jaffe *et al.*, 2006), 82% of parents surveyed believed gene therapy to be the most important area of research for those with CF. The prospect of gene therapy treatment being developed offers hope to both CF patients and their families and it is proposed that this prospect helps them to feel less afraid of the future (Gotz & Gotz, 2000).

Although there has been disappointment about the uncertainty regarding the application of gene therapy (Gotz & Gotz, 2000), researchers, patients and families still have an investment in seeing a positive outcome. As barriers to effective gene therapy are overcome, the following hope may be realised:

“CF researchers, clinicians, parents and patients will increasingly be able to imagine a time when a child growing up with CF will breathe with lungs similar in function to the lungs in normal children.”
(Parsons, 2005, p.96)

Participant Expectations of Gene Therapy in Gene Therapy Trials

There has only been one published study to date on a CF gene therapy trial that has investigated psychological factors involved in participation (Blair *et al.*, 1998). Qualitative and quantitative methods were used to assess the expectations, knowledge and psychological functioning of sixteen CF participants in a single dose nasal gene therapy phase I safety trial (Blair *et al.*, 1998). As reported in the study “most participants” had a realistic understanding that they could not expect personal clinical benefit from participating on the safety trial. Whilst it is unclear how many participants this constituted, it was also reported that thirteen participants expected to benefit personally from gene therapy in the future. This led researchers to conclude that participation in the trial led to slightly raised expectations of personal future benefit.

A more recent study was undertaken by Thomas *et al.* (2007). This was the first empirical investigation of whether adults with CF had realistic expectations of gene therapy. A single-site investigation of patients’ knowledge and opinions of gene therapy for CF was undertaken with 72 adults completing questionnaires. This covered whether patients’ knowledge of gene therapy was realistic, what their sources of information on gene therapy were, whether patients wished to know more about gene therapy and what their expectations of gene therapy were. Amongst the findings was that 46% of respondents believed that receiving gene therapy treatment for themselves

was unlikely but 77% believed that that children under five and the unborn were most likely to benefit.

No participant was enrolled on a gene therapy trial. This study was replicated and extended to cover four sites and participants completed a clinic-based questionnaire which yielded both quantitative and qualitative data. The findings have been presented at the European CF Conference (Richards *et al.*, 2008) and the study is currently being written for publication in full (A. Duff, personal communication, 17 June 2009). Although 75% of participants indicated interest in how gene therapy might work and 74% were interested in its potential benefit for them, none of the 266 participants was participating on a clinical trial for gene therapy (A. Duff, personal communication, 17 June 2009). This leaves a gap in knowledge regarding what participants with CF expect of gene therapy as they take part in a gene therapy trial from which clinical benefit is anticipated.

1.11 Rationale for the Current Study

Patients with CF are closer to gene therapy than ever before. The gene therapy trial is of importance because of the amount and type of data it will generate as the biggest gene therapy trial to date. It is also the first trial of its kind that will give participants gene therapy on multiple occasions, which may result in clinical benefit. However, the magnitude of any clinical benefit from the trial is as yet unknown and the trial is designed to allow investigators to look for changes that indicate clinical benefit (J.A.Innes, personal communication, 24 June 2009).

Expectations of the participants in the Run-in study have not been explored regarding outcomes of the gene therapy trial. There has been no study to date exploring the psychological impact of participants in a preliminary trial awaiting selection for a gene therapy trial. The current study will therefore provide data from participants recruited to the Run-in study in which medical measurements and participants are being selected for the gene therapy trial

1.12 Aims of this Study

The current study aimed to discover the following:

1. Expectations that participants on the Run-in study had of participation in the gene therapy trial.
2. Any misconceptions that participants may have had of gene therapy treatment.
3. Participants' general expectations of gene therapy.
4. Whether participants' expectations of gene therapy treatment had changed since they started participating in the CF Run-in study.
5. Whether participants had experienced any physical or psychological difficulties or benefits whilst participating on the Run-in study.

This study also aimed to identify whether there were any particular areas in which participants required psychological support e.g. if not selected for the gene therapy trial. Qualitative methodology was selected to allow for exploration of these aims and to provide evidence. The use of this method will be described in detail in the following chapter.

It was hoped the current study would make a small contribution to the evidence base by discovering expectations that participants currently participating in the Run-in study had of the trial and of gene therapy in general. This was a novel area of research with such a cohort. It was also hoped that the study would identify psychological factors involved in the process of anticipating selection for the trial.

2 METHOD

This chapter provides an overview of the research design and methodology selected for the study. It also outlines how the quality of the research was managed in terms of transparency and rigour.

2.1 Research Design

The main aims of the study were to discover the expectations that participants resident in Scotland and northern England recruited for the CF Run-in study had of the gene therapy trial and of gene therapy in general and to ascertain whether these expectations changed during their participation in the CF Run-in study.

It is important that the research method selected is appropriate for the questions being investigated (Barker *et al.*, 2002). A qualitative rather than a quantitative approach was chosen since it can uncover the nature of people's experiences and perspectives as yet little explored in research (Parker, 2005). There has been little research into psychological factors involved in participation in gene therapy trials for CF. It was anticipated that a richer description of participants' expectations would be yielded by using a qualitative approach than by using the fixed response options of a quantitative measure.

Following Burman (1994), a semi-structured interview was designed to allow for exploration of issues that might be too complex or not be sufficiently identified to allow investigation by quantitative methodology. A well designed semi-structured interview with appropriate use of open questions allows for the generation of a wide range of

responses (Parker, 2005). Because it is semi-structured, it is also an open and flexible research tool (Burman, 1994). A semi-structured interview was selected as a methodological tool to allow the interviewer to respond sensitively to participants' concerns as they arose through interview and thus also record perspectives that were not anticipated, thereby enhancing the richness of the data.

2.1.1 Grounded Theory

The current study was based on the constructivist version of grounded theory proposed by Charmaz, which acknowledges that the researcher aims towards an interpretive understanding of the data (2000). Following this philosophy, knowledge is mutually created by both the researcher and the research participant (Charmaz, 2000). The current study also draws upon guidelines set out by Strauss & Corbin (1998). The rationale for the researcher's choice of approach is outlined below with the qualification that there is a degree of flexibility in the use of grounded theory methods (Annells, 1997; Charmaz, 2006; Glaser and Strauss, 1967).

2.1.2 Epistemological Issues

The choice of a particular research method can be influenced by the researcher's epistemological position on how knowledge is understood and reached. For example, there may be a bias towards a positivist, quantitative approach if a researcher believes that empirical methods uncover an objective reality (Murray & Chamberlain, 1999). Yet there is an increasing challenge to the claims of objectivity in the positivist paradigm (Murray & Chamberlain, 1999). Whilst this debate is outside the scope of the current study, it is important to acknowledge that researchers are located within a diversity of perspectives and assumptions. However, the researcher should be guided in

the choice of research methods by the nature of the research question (e.g. Strauss & Corbin, 1998). The research method itself should not be held in special regard (Barker *et al.*, 2002) such that:

“A thousand-word description is no more valid a “picture of the person” than a single score on a standardised test.” (Gergen & Gergen, 2000, p.1027).

All methods have their relative advantages and disadvantages and therefore an informed choice can be made about the best fit between purpose of the study and method (e.g. Barker *et al.*, 2002; Kvale & Brinkmann, 2009). A qualitative approach was selected for the current study (See Section 2.6.1: Approach to Conducting a Semi-structured Interview) after formulating the research questions and clarifying the purpose of the study (Kvale & Brinkmann, 2009). Whilst the researcher was aware that both Interpretive Phenomenological Analysis (IPA) and grounded theory could capture the nature of participant expectations of gene therapy and had structured guides for novice qualitative researchers, she chose a grounded theory approach because she also wanted to map social processes in the nature of participation in trials (Charmaz, 1995; Dallos & Vetere, 2005). The researcher was aware that if not conducted analytically in order to develop theory, the approach could yield a descriptive, systematic map of concepts and categories (Willig, 2001). However, Charmaz (2006) has also highlighted that a grounded theory approach is valuable for producing descriptive studies, although descriptive findings do not result in hypotheses or make explicit predictions.

2.1.3 Grounded Theory Methods

Grounded theory methods were originally outlined by sociologists Glaser and Strauss in the 1960s. Grounded theory was developed as a challenge to the prevailing quantitative,

positivist practice in which hypotheses were logically deduced from existing theories (Charmaz, 2006, p.4). Qualitative methods were often used in the initial stages of research in order to refine quantitative methods for subsequent more “rigorous” research (Charmaz, 1995, p.29; Charmaz, 2006). Glaser and Strauss (1967) proposed a revolutionary, systematic and concurrent approach to data collection and analysis in order to develop novel theories from research that is grounded in, or drawn from, the data.

Different schools of thought have arisen concerning grounded theory methods. Strauss and Corbin’s (1990) co-authored work *Basics of Qualitative Research: Grounded Theory Procedures and Techniques* refined the techniques of grounded theory. There is some debate as to whether this book and the later second edition of their work (Strauss & Corbin, 1998) develops grounded theory methods or offers technical procedures that are essentially different from the original conception of the method (Charmaz, 2000). Although Glaser (1992) vigorously contested the formulaic techniques of Strauss and Corbin, the latter’s techniques may help novice researchers to better understand the process of data gathering and asking questions of the data (Charmaz, 2000). The approach of Strauss and Corbin leans towards a positivist stance in which data is seen as being real yet it also recognises interpretation of data by the researcher. The stance of Charmaz (2000) is that the data are reconstructions of experience rather than the actual experience itself. Therefore the researcher’s interpretation of the area under study is in essence a construction rather than an objective reality to be discovered (Charmaz, 2006). This researcher recognises that interviews themselves may contain constructions, with any interpretation of these being constructions of constructions.

2.1.4 Process of Grounded Theory

The analysis begins with the process of coding emerging data as it is collected. Therefore data collection and data analysis are concurrent. Coding involves studying the data in order to separate it into discrete labels for each action, event and process. As such, coding emerges from the data with categories being created of actions, events and processes which share common features or characteristics (Charmaz, 1995, p.37). When categories are descriptive they work as “descriptive labels.” As the process of analysis develops, the researcher identifies categories at a more abstract “analytic” level which interpret examples of data (Willig, 2001, p.33). Categories are conceptual in the sense that they are defined specifically in terms of their properties i.e. characteristics or attributes (Dey, 1999).

Using a process known as constant comparative analysis, the researcher identified similarities and differences regarding emerging categories (Willig, 2001). Comparisons were made within the same individual’s account, between different individuals, and between data within separate categories (Charmaz, 1995). This allowed for the construction of subcategories and for the integration of subcategories into categories. The researcher looked for instances of “negative cases” where instances did not fit into emergent categories (Willing, 2001, p.35). This set limits on the emerging theory and allowed it to represent the complexity of the data from which it was drawn (Willig, 2001). Following the suggestion by Charmaz (2006) for memo-writing, the researcher successively maintained notes of research and analysis which prompted the researcher to a more analytic level of theory development.

Theoretical sensitivity occurs when the researcher is sensitised to the data in terms of how to modify or enrich the emerging theory. Theoretical sampling occurs when the researcher is refining categories and discovers gaps in the data which require more data in order to make categories more definitive and therefore refined (Charmaz, 2000). It also serves to define the links between categories (Charmaz, 2000). Finally, theoretical saturation occurs when no new categories are constructed and existing categories can no longer be questioned or expanded (Willig, 2001). Some have questioned whether pure saturation can realistically be achieved (Dey, 1999; Willig, 2001; Charmaz, 2006) but a reasonable approximation to theoretical saturation may be an achievable goal.

2.2 Research Tools

2.2.1 Demographics Sheet

This was designed by the researcher to gather basic demographic information about participants. The information was gathered from interviews and from Run-in study notes under supervised access by the research team. The information included date of birth, time of diagnosis and lung function at the first Study Visit. It cannot be included in full here because of confidentiality issues. However, an outline of the demographics sheet has been included as an appendix (See Appendix 1) and information from it has been presented in the Results (See Section 3.1: Participant Information, Table 1). As time of diagnosis would have indicated disease severity and may have influenced the researcher's expectations regarding the interviews, these details were only confirmed after interviews had taken place. This was in order for the researcher to ask questions that were not influenced by prior anticipation of the participant's response.

2.2.2 Semi-structured Interview

A semi-structured interview schedule was compiled by the researcher and consisted of five core questions. This schedule offered a useful structure for the researcher, who was new to qualitative research, since initial questions devised in advance can ensure the avoidance of leading questions or of questions that would result in minimal responses (Smith, 1995). The five core questions were devised to address the aims of the research. However, in keeping with a grounded theory approach, processes of data collection and data analysis were linked throughout the research process to develop theory (e.g. Glaser, 1992). Thus the researcher developed or revised questions for subsequent interviews that enabled further exploration of emerging categories (e.g. Glaser, 1992). This included additional ways of asking the same question to facilitate exploration. A copy of the schedules used in interviews with Participant 1 and 12 is enclosed in Appendix 2, with additions to the schedule in italics.

Questions from a previous study of expectations of gene therapy in CF were considered in developing the current questions in the semi-structured interview (Blair *et al.*, 1998). The researcher amended these questions to facilitate exploration of issues relevant to the current study aims. The aims and corresponding questions are shown in Figure 1 .1 overleaf:

1. Aim:	To discover participants' expectations of the gene therapy trial.
Question:	If you are selected for the gene therapy trial, what do you expect the outcome of the trial to be for you personally?
2. Aim:	To discover any misconceptions that participants may have of gene therapy.
Question:	What do you know about gene therapy?
3. Aim:	To discover the wider expectations that participants have of gene therapy.
Question:	What difference do you think that gene therapy treatment will make to the lives of people with CF in the future?
4. Aim:	To discover if participants' expectations of gene therapy treatment have changed since starting on the Run-in study.
Question:	Have your expectations of gene therapy treatment changed since you started participating in the CF Run-in study?
5. Aim:	To discover any difficulties (physical or psychological) or benefits that people experience whilst participating in the Run-in study for the gene therapy trial.
Question:	How is taking part in the CF Run-in study affecting you?

Figure 1.1: Questions addressing study aims

2.3 Ethics

Before any research with participants is undertaken, consideration must be given to ethical implications arising throughout the research process. Participants are to be protected from harm at all times, with the added aim of preserving their psychological well-being, health, dignity and values (Tindall, 1994, p. 152). Because this study aimed to ask participants with CF potentially sensitive questions, very careful attention was given to ethical issues during the process of research design. This helped to sensitise the researcher to areas which required careful thought and to ensure that the research was

undertaken in accordance with the ethical standards of the University of Edinburgh (2002) and the British Psychological Society (2005).

2.3.1 Ethical Issues

The researcher considered the following closely intertwined ethical issues relevant to this research:

- Acquiring informed consent
- Guaranteeing confidentiality
- Managing participants' potential fatigue
- Managing potential distress of participants
- Considering potential non-selection for the gene therapy trial
- Keeping home visits safe

2.3.2 Acquiring Informed Consent

To facilitate mutual respect and to undertake research with integrity, there needs to be full disclosure to the participants of the nature of the research. This involves the role of the researcher, the purpose of the research, the requirements of participation, the style and length of interview, the number of participants being recruited and the management and use of data (Tindall, 1994).

To facilitate informed consent, a Patient Information Sheet (See Appendix 3) and an invitation letter (See Appendix 4) were sent to all identified patients participating on the Run-in study (See Section 2.5.4: Recruiting Identified Participants). Patients had at least one week to read the information regarding the study and to discuss any questions or issues with friends, family members, the researcher or any relevant professional

before deciding whether or not to participate (See Section 2.5.4: Recruiting Identified Participants). In addition, potential participants were given the contact details of a Consultant Physician in Respiratory Medicine, who was available to provide independent information about the research study.

All patients had given informed consent for participation in the Run-in study. These patients had already been screened to ensure that none had a history of cognitive difficulties or severe psychiatric illness. Participants in the current study indicated that they wished to participate by telephone or by using the response slip on the invitation letter (2.3.4 Recruiting Identified Participants). When meeting participants, prior to any interview being undertaken, the researcher ensured that any questions about the study were answered and that the participant understood the role of the researcher, the nature of the study and the nature of participation. Participants were informed of the number of participants recruited and of the management and treatment of data and results.

The researcher also informed participants of their right to withdraw from the current study at any time. The researcher reiterated that continuing or future care was not dependent upon participation in the interview. She also reiterated that she was not part of the CF Run-in research team and that any selection procedures for the gene therapy trial would not be influenced by their participation or otherwise in the current study. It was ascertained by the researcher whether consenting patients still wished to be interviewed. A consent form was then completed and signed by participants and counter signed by the researcher (See Appendix 5). The researcher was not involved in the clinical care of any of the participants in the Run-in study.

2.3.3 Guaranteeing Confidentiality

Patients were informed via the Patient Information Sheet that the interviews would be strictly confidential. Although the patients' hospital consultants and general practitioners (GPs) were informed of patients' participation in the study (See Appendix 6), the content of interviews remained strictly confidential. At the research interview, the procedure of protecting confidentiality was reiterated with the exception of where there were issues for the safety or wellbeing of the patient or others. It was also restated that only the researcher would have access to a portion of the recorded interviews, with her research supervisors having access to anonymised versions of a portion of the interviews for transcription purposes.

Following data collection, all audio recordings of the interviews and interview transcripts were stored on password-protected computers located in the locked room of the researcher. A portion of the transcripts used for coding purposes was stored on password-protected computers by both supervisors in their locked rooms. No patient names were used during the interviews and any identifying information was removed from transcripts. The researcher used a code known only to herself to identify transcripts. All documents pertaining to the study that contained identifying information were filed in a locked cabinet in the Clinical Psychology office at the hospital. Only the researcher and clinical supervisor had access to this. Christians (2000, p.139) warns that watertight confidentiality may be an impossibility in that pseudonyms for research participants may be recognised by interested parties. Whilst pseudonyms were not used, the researcher made every effort to remove potentially identifying features from participants' quotations before their inclusion in the completed thesis. This will be the same procedure for anticipated presentations that are based on this thesis.

2.3.4 Managing Participants' Potential Fatigue

Once the researcher was satisfied that the participant was not currently experiencing a chest infection, each interview was preceded with the reminder that the interview could be stopped at any point should the participant become tired or wish to stop for any other reason. The interview could then be rescheduled if desired by the participant. Participants were also reminded that the interviews were not fixed in terms of duration but would not exceed one hour. This advice was included on the Patient Information Sheet. Whilst no participant requested that the interview be stopped, the researcher closely observed participants' energy levels and on one occasion enquired whether the participant was able to continue. Further, to minimise risks of potential fatigue, interviews were not scheduled for days when participants had Run-in study visits. None of the participants were currently involved in any other psychological research. Interviews were also conducted at a time and location that was convenient for participants, recognising the need to minimise additional disruption to work, education and free time.

2.3.5 Managing Potential Distress of Participants

The researcher had experience of working with the emotional distress of patients in her role as a trainee clinical psychologist. The researcher was also undertaking a year long specialist placement with adults with CF and had knowledge and practice of working with issues specific to the condition.

Prior to interviews taking place, it was decided that the researcher would stop an interview should a patient become distressed. It would then be ascertained if the patient wished to continue with the interview. If the interview was continued with the patient continuing to be distressed, the researcher would discuss with them sources of support

including potential referral to their local CF psychology service. A system had been put in place where local CF psychologists were prepared to offer support and back up to any participants who needed it. This had been developed by the researcher in conjunction with her clinical supervisor and with other CF psychologists. One participant became distressed during the interview due to the start of the gene therapy trial having been delayed. However, she did not wish to be referred to psychology, preferring the support of her husband.

2.3.6 Considering Potential Distress at Non-selection for the Gene Therapy Trial

The researcher was aware of participants' potential distress at the prospect of not being selected for the gene therapy trial. Whilst distress was not inevitable, it was decided that the participant be allowed to raise any issues relevant to this situation. The researcher monitored the effect of the interview on the participant and was vigilant to both verbal and non-verbal signals that indicated possible distress. In addition, Kvale and Brinkmann (2009) raise the dilemma of a potential quasi-therapeutic relationship developing in which participants may share information that they retrospectively regret. Following Kvale and Brinkmann (2009), the researcher was aware that sensitive issues could suddenly arise during interviews. In the event she did not want to disregard the participant's privacy by inappropriately and unethically using a therapeutic approach. As above (See Section 2.3.5: Managing Potential Distress of Participants), she offered to refer the participant to psychology services.

2.3.7 Safety Issues Surrounding Home Visits

Because interviews were scheduled at a time and place convenient to the participant, and reasonable to the researcher, five of the twelve participants requested a home visit

for the interviews. To ensure the researcher's safety, the clinical team were consulted prior to any home visit to determine whether there would be any likely safety issues should a home visit be undertaken. The researcher also provided her clinical supervisor with a schedule of home visits and telephoned her clinical supervisor following each visit. This was in order to confirm that the visit had gone safely and to alert her to any issues related to the visit.

2.3.8 Ethical Approval

Ethical approval was granted by local NHS Research and Development Management who expressed their satisfaction with the study design on the 3rd December 2008, pending full ethical approval. Full ethical approval was granted on 16 January 2009 following minor amendments. A copy of the approval letters can be found in Appendix 7. Identifying details of the centre where the researcher was based have been removed but the original approval letters can be produced if required.

2.4 Pilot Study

Prior to recruitment letters being sent out, two pilot interviews were undertaken with two volunteers, neither of whom had CF and both of whom were physically well. One interviewee was in his sixties and employed in the mental health field and one was in her thirties and employed in education. These interviewees were asked to use role play since three of the interview questions presupposed that the respondent would have CF and was involved in the CF Run-in study. The researcher considered it ethically inappropriate to conduct a pilot interview with CF patients who were not recruited for the CF Run-in study since they would not have the possibility of being selected for the multi-dose gene therapy trial. Although the two interviewees did not have CF, the pilot

interviews offered useful preliminary insights into the interview process and into the development of the researcher-interviewee relationship and its influence upon what is said during the interview.

The pilot interviews also afforded the researcher the opportunity to practise asking the questions and to be guided by the interviewees as to the pace of delivery. They also allowed the researcher to perceive individual differences in responding to the questions.

The researcher practised using the digital voice recorder (Olympus VN-1000PC) intended for use in the interviews and its attendant computer software. She had the opportunity of doing some initial transcribing before recruitment took place. Whilst there may be a place for taking notes during interviews, using recording equipment enabled the researcher to engage with the interviewee. Furthermore, the researcher was not trained in shorthand. However, the researcher took notes shortly after interviews to record any information not captured on the audio recording e.g. before or after interview, body language etc.

Whilst the researcher was not herself interviewed using the schedule, she considered her own responses to the questions prior to recruitment. She found this process sensitised her as to how the questions could be perceived by interviewees. Because the researcher found that she required time to formulate responses to the questions, she ensured that she gave participants enough time in which to process their answers.

2.5 Participants

2.5.1 Inclusion Criteria

Inclusion and exclusion criteria were based upon those used in the CF Run-in study. The researcher included the additional criterion that participants should not be currently participating in any other research of a psychological nature. This was due to concerns that the participants could potentially be overburdened by too many research demands, exacerbated by the daily treatment burden that many CF patients experience. All participants on the CF Run-in study were fluent in English. The criteria were as follows:

- Diagnosed with CF.
- Aged 16 or above.
- Participating in the CF Run-in study in Scotland.
- Not currently taking part in any other psychological study.
- Neither awaiting referral for a lung transplant nor having been referred for such.
- Not having had a lung transplant.

2.5.2 Exclusion Criteria

The following exclusion criteria were used to ensure fitness for participation in the interview:

- An increase in CF symptoms e.g. increased wheeze or breathlessness in the preceding two weeks before interview.
- The use of extra antibiotics for the two weeks prior to interview.

2.5.3 Identifying Suitable Participants

The Run-in study is a UK wide study with the two main bases being London and Edinburgh, with Edinburgh recruiting participants from Scotland and the North of England. This study is limited to those patients recruited via the Edinburgh site due to geographical considerations for the researcher. There was discussion with the Edinburgh-based CF Run-in team (which consisted of the research manager and two research fellows working with the Gene Therapy Consortium) about which CF Run-in participants would meet the criteria for the current study. Because of the research fellows' concern not to jeopardise the continuation of three participants who were considering withdrawing from the Run-in, these patients were not invited to participate in the current study. It was ascertained that forty-two participants in the Run-in study met the study criteria.

2.5.4 Recruiting Identified Participants

The Run-in study research team thought that the initial approach to patients should be made through the principal investigator from the Run-in study. This was to help patients understand why they were being contacted about the current study and that the invitation to participate had the support of the Run-in study. Information about the study was given to the principal investigator, who jointly drafted the invitation letter with the researcher. However, the letter stressed that the researcher was not part of the Run-in study and that accepting the invitation to participate would not influence patients' chances of selection for the gene therapy trial.

The researcher sent out the invitation letter signed by the principal investigator to 39 patients. The Patient Information Sheet was included with the letter. The remaining

three identified patients were scheduled to attend a study visit, where they received an envelope containing an invitation letter and Patient Information Sheet from the research fellows. Due to an initial low response rate, a repeat invitation letter and Patient Information Sheet were sent out at a later date in the study to those who had not responded by telephone or e-mail or by returning the response slip attached to the invitation letter.

2.5.5 Researcher Contact with Consenting Participants

All but one consenting participant returned the response slips. These were telephoned to arrange an appointment for an interview. Before an appointment was arranged, the researcher again outlined the nature of the study to which they had consented and answered any questions participants raised. The researcher also checked whether they still wished to participate in the study. For the one participant who gave verbal consent by telephone, the researcher followed the same procedure.

Appointments were arranged for dates that did not coincide with CF Run-in study visits and at times and locations that were convenient to the participants. As outlined earlier (See Section 2.3.7: Safety Issues Surrounding Home Visits), home visits were undertaken only after they were assessed as being safe. Participants were asked to contact the researcher should the interview appointment prove not to be convenient for them. The researcher telephoned each consenting participant approximately two days prior to the interview both to confirm the time and place arranged and to check whether the participant was in stable health.

2.5.6 Notifying Medical Professionals About Recruitment

The researcher sent a letter to the General Practitioners and Hospital Consultants of all consenting patients. This was to notify them that their patients had given consent to undertake the current study. General Practitioners and Hospital Consultants were invited to contact the researcher should they have any questions regarding the research and what it entailed for their patient.

2.5.7 Summary of Recruitment

Altogether, forty-two CF Run-in participants were identified by the Edinburgh CF Run-in research team as being potentially appropriate for the current study. An invitation letter and Patient Information Sheet were sent out by the researcher to thirty-nine patients. Three participants received an invitation letter and Patient Information Sheet given by the research fellows at their study visit because they were due to attend at the time the letters were being sent out. There were four participants who indicated via the response slip that they did not wish to participate and there was one query by telephone for further information which did not result in participation. Due to an initial slow response rate, the invitation letter and Patient Information Sheet were sent to those who had not already indicated any response. Twelve participants altogether were recruited by letter to the current study. The researcher telephoned each participant who had consented by response slip to arrange an interview. There was only one participant who telephoned to give verbal consent during which conversation the researcher and participant arranged an interview. The researcher sent a letter to the General Practitioners and Hospital Consultants of all consenting patients. All participants gave informed consent. No participants withdrew therefore twelve participants completed the current study.

2.6 Interviews

2.6.1 Approach to Conducting a Semi-structured Interview

The researcher's epistemological assumptions about the type of knowledge obtainable in a qualitative interview are partially captured in the belief that an interview is essentially "intersubjective interaction" (Kvale, 1996, p.66). As such, qualitative interviews are influenced by the viewpoint and the values of the investigator (Kvale & Brinkmann, 2009) and by the construction of meaning by both participant and interviewer. For example, participants can reformulate questions during the interview and then answer these, even though the interviewer's questions should lead the interview more in order for it to be "successful" (Mishler, 1985, p.54). Through the process of reformulation, both interviewers and participants try to establish mutually understood meanings (Mishler, 1985).

The actions and words of participants are located within a particular context. This is described as the context of other meanings, beliefs, values and practices that participants will hold (Kvale & Brinkmann, 2009). The researcher was aware that gender, class, age and race amongst other factors would be part of the personal and social context of the participants. The researcher also needed to maintain awareness of how she might also interact within the interview-participant relationship. The researcher tried as far as possible to minimise potential structural power relationships (Burman, 1994). Mishler (1985, p. 126) suggests that participants be seen as research collaborators i.e. as full participants in the analysis and interpretation of data. The researcher sent the participants a copy of her proposed themes before the final write-up of the research so that amendments could be made if warranted (See Section 2.9.1:

Validity). Following Glaser and Strauss (1967), the researcher set out to inductively develop a theory grounded in the data from the interviews.

2.6.2 Interview Procedure

Prior to the interview commencing, the researcher briefed participants regarding the nature of the study. A Patient Information Sheet was also available should participants need to refer to this again. The researcher allowed opportunity for participants to raise any questions relating to the study. The consent form was then completed and countersigned by both participant and researcher. Participants were invited to inform the researcher if they became fatigued and wished to reschedule. The researcher referred again to the interviews being recorded and emphasised confidentiality and anonymity in connection with written transcripts and recordings. Indeed, although access to the audio files was protected, the researcher made participants aware that she would not use their names during the interview as an extra precaution.

Prior to the interview being conducted, the participant and the researcher did a very brief pilot recording on the digital voice recorder to ensure that the equipment was recording correctly. These pilot recordings were erased following the interview. The researcher was aware of maintaining as relaxed an atmosphere as possible to put participants at their ease. Part of this process involved showing a genuine interest in the participant and in his or her responses and minimising discomfort when there was a perceived power differential e.g. when the participant assumed superior knowledge of gene therapy on the part of the researcher, the latter stated that this was not the case. The timing in delivery of the questions was regulated so that the participant had time to respond to, or to query, what was being asked. The research interviews varied in length

from twenty-two minutes and five seconds to fifty-five minutes and twenty-seven seconds with the average interview time being thirty-two minutes and twenty-nine seconds.

In keeping with Kvale's (1996) advice to debrief participants following interview, all participants except one were invited to comment on their experience of being interviewed and to ask questions about the interview process or the study. The one exception was an interview in which the participant became upset. The research interview was ended and the researcher created space to discuss the possibility of future support for the participant. This enabled the participant to step out of the interview process with dignity.

The researcher outlined how she would disseminate findings and highlighted that she would be more than happy to meet again with the participants individually to discuss the findings or to discuss these by telephone or e-mail. Immediately following the interview, the researcher recorded her thoughts and feelings with reference to the interview in her reflective diary. She also recorded aspects of the methodology that she felt could be improved e.g. not asking one question immediately followed by another related question, thus allowing the participant space for reflection as suggested by Kvale & Brinkmann (2009).

2.7 Data Management

Following each interview, the researcher downloaded the audio file from the digital voice recorder onto a password protected computer. The file was then deleted from the digital recorder. Codes were used to identify the files and only the researcher had

access to the coding system. The interviews were then transcribed verbatim, with any identifying features excised from the transcripts. The researcher then double-checked each transcript for accuracy by checking the text against the recorded interview.

Transcripts were formatted with wide margins, which allowed initial coding on the left hand side and questions, memos and focused coding on the right hand side. Following Parker (2005), pauses were marked and the word “unclear” was used to mark sections that were difficult to understand.

2.8 Stages of Analysis

Qualitative analysis was carried out on data from the research interview transcripts, on notes in the researcher’s reflective diary and on memos. The researcher began the analysis whilst transcribing research interviews as she concurrently started to notice occurring themes. Formal analysis began with coding. This is a fundamental process in grounded theory during which one defines what is occurring in the data and is thereby guided in developing theoretical categories which enable a theoretical understanding of the process being investigated (e.g. Chamberlain, 1999; Charmaz, 1995). Charmaz (2006) directs the researcher to interpret participants’ tacit meanings within data. The researcher was guided in her approach to coding by using the guidelines of Strauss and Corbin (1998) and Charmaz (2006).

2.8.1 Initial Coding

Following Strauss and Corbin (1998), text was initially coded by the researcher line-by-line and by hand. As recommended by Charmaz (2006), the researcher tried to understand participants’ views and actions from their perspective, paying close

attention to the context of the data and participants' implicit meanings. Codes used the gerund form of the verb as much as possible to allow the process to emerge rather than being descriptive and to keep the analysis grounded in the data (Charmaz, 1995). The researcher also frequently used codes based on the words of participants themselves, although line-by-line coding helped the researcher not to become immersed in participants' accounts but to break the data into codes critically and analytically. Initial codes were written in the left-hand margin of the page, with the right-hand margin being used for more frequent codes, areas of interest and observations for later development into memos (See below). The researcher constantly compared sections of data side-by-side within transcripts and between transcripts. An example of initial coding is provided in Figure 1.2 and a detailed example is given in Appendix 8.

CODING	INTERVIEW TRANSCRIPT	MEMO
Expecting a normal life for future generations	Hopefully it will mean that people with CF can just have a quite normal life [with future treatment]	This was mentioned by Participant 8
Understanding of "normal"	Well, normal if terms of lifespan and you can play all the sports you want to play.	Participant's assumptions behind "normal"
Explaining personal impact of having CF	None of this happened to me but you do hear about people who have to put up with an awful lot.	Participant experience of CF seems to differ between early and late diagnosis - Participant 1 also has late diagnosis.
Expressing queries over her own understanding	I don't fully understand whether the gene therapy would only treat the breathing symptoms or whether it would treat other symptoms as well	Full versus partial cure?

Figure 1.2: Example of Initial Coding

2.8.2 Qualitative Data Analysis using Software Support

Using Nvivo8 helped the researcher to become more immersed in the data. After initial coding by hand, the codes were entered into the software package NVivo 8 (QSR International Pty. Ltd., 1999-2009) to assist with qualitative analysis and to help to keep a record of analysis done. The software package provided a visual representation of the data entered. The researcher continued to make comparisons between instances of data and to develop categories and subcategories. This was helped by using existing memos and by drafting new memos. The memos were notes of the researcher's observations and interpretations whilst coding. An example of an early memo is in Figure 1.3 below:

Participant 1
Keeping one's expectations realistic
<u>Extract:</u> <i>I try to keep people's expectations realistic. I try to keep my own realistic not least because I may not be selected for the actual therapy itself.... so I'm quietly confident but if works out that's absolutely super, you know. (lines 53-62)</i>
<p>The participant expressed his ambition to be fitter and healthier by being on the gene therapy trial but recognised that he needs to be realistic about any personal outcome of the gene therapy trial. He is also actively trying to keep the expectations of others realistic. The participant identifies the possibility that he might not be selected for the gene therapy trial. He likes the odds of being selected and he is quietly confident of selection. However, he contrasts this with "but" i.e. if it works out, it will be "absolutely super." There seems to be a process of pulling back from complete hope that the trial will be beneficial for him and yet the hope of success is strong.</p>

Figure 1.3: Memo: Keeping one's expectations realistic

2.8.3 Focused Coding

The researcher moved on to focused coding which involved selecting the most frequent initial codes to categorise data and using these codes to compare and understand larger segments of data. This took the analysis onto a more theoretical level as the codes are more conceptual than line-by-line coding (Charmaz, 2006). The researcher used focused coding to further refine categories.

2.8.4 Axial Coding

The researcher used axial coding to reassemble data that were broken down into distinct pieces during initial coding. Through constant comparison between pieces of data, the researcher validated her comparisons thereby furthering her analysis (Strauss & Corbin, 1998). The researcher brought the data back together by linking categories and subcategories and by specifying their dimensions and properties (Charmaz, 2006). Through this process, a large amount of data was organised and put together in a new way.

2.8.5 Selective Coding

In selective coding, the theory was integrated and refined as the researcher selected an emerging central concept that was able to draw all the other categories together. This created an overall explanatory concept of the process being studied (Strauss & Corbin, 1998). Nvivo8 was used to draft models of the central concept and its relationship to other categories. Memos were used to build links between categories and to develop the researcher's ideas and the explanatory power of the central concept (Strauss & Corbin, 1998).

2.8.6 Theoretical Saturation

The researcher was able to collect data until she was largely satisfied that no new properties of categories would arise, although fresh theoretical insights could still have occurred.

2.8.7 Writing This Manuscript

The researcher continued to undertake data analysis as she wrote this manuscript. This helped with the furtherance of insights, the development of new ideas and the creation of a theoretical framework to explain the researcher's analysis (Charmaz, 2006). The researcher continued to develop her analysis by gaining further insights in writing several drafts of the manuscript.

2.9 Warranting Quality in Qualitative Research

The management of quality in qualitative research is a highly pertinent topic and consideration needs to be given as to how questions of credibility can be answered since there is debate whether qualitative methods can be assessed with the same evaluative criteria as quantitative methods e.g. reliability, validity and replicability (Dallo & Vetere, 2005; Flick, 2007). Nevertheless the following criteria can be found as approaches in qualitative research:

- Validity
- Transparency
- Reflexivity
- Triangulation

2.9.1 Validity

If qualitative research is to be conducted plausibly, the researcher must monitor how the research has been conducted and to challenge himself or herself in this (Tindall, 1994). The researcher recognised that her interpretations of participants' experiences would be influenced by her assumptions and should therefore be "open to challenge" (Dey, 1999, p.136). Regular joint meetings between the researcher and her supervisors provided the opportunity for the researcher to evaluate her own influence in the construction of findings.

Following Flick (1998), the researcher sought to ground her interpretations in participant accounts with quotations being incorporated into the results to show the source of the researcher's interpretations. Contextual validity was also involved with the researcher checking with participants whether the research account was recognisable (Dallos & Vetere, 2005; Tindall, 1994). One response to date has been received by the researcher.

2.9.2 Transparency

For Dey (1999), the value of a transparent process is implied when grounded theory does what it sets out to do i.e. when an account is grounded conceptually in the research data. The researcher kept a record of how interpretation was undertaken throughout the research process through the use of memos and written notes. This highlighted questions that the researcher asked of the data and allowed her to record her reflections and observations of the data and of the research process. The researcher noted decisions concerning the development of her ideas which enhanced transparency. Transcripts of research interviews and related memos will be made available for review upon request.

2.9.3 Reflexivity

In using reflexivity, the process through which the researcher produces the report material and analysis is made explicit. The key position of the researcher is acknowledged in the construction of knowledge (Tindall, 1994). The value of reflexivity in qualitative research has been emphasised in enhancing validity (e.g. Charmaz, 2006; Parker, 1995; Willig, 2001). The inclusion of analysis in a research report allows readers to judge the content within “the context of the perspectives and assumptions by which it was shaped” (Marshall, 1986, p.195). The researcher’s analysis has been included in the Results and Discussion sections of this report.

Tindall (1994) highlights the importance of personal reflexivity in recognising how personal interests and values affect the research process. In keeping a reflective diary a record can be kept of how findings were interpreted and how the researcher’s belief has influenced the research. An entry from the researcher’s reflective diary is provided overleaf in Figure 1. 4.

<p>Interview with Participant 12</p> <p>Location: Hospital room</p>
<p>The participant seemed very relaxed. He came across as very articulate and had clearly done some thinking on gene therapy. It was a reflective process for him as he commented on the fact that the interview was offering him the chance to think about things. He realised that he hadn't asked some questions which might have been of help, perhaps prompting him to go and ask the questions at a later stage once he knew whether he'd got on to the next stage of the trial. It was a very interesting interview for me. In a way it's harder with someone who is articulate and bright because you can get sparked into a conversation of mutual interest or value the way they say something though hopefully not to the exclusion of content!</p> <p>I deliberately tried not to say too much during the interview and to ask questions rather than to summarise too much. Also to give him space to say more!</p>

Figure 1.4: Example from researcher's reflective diary

2.9.4 Triangulation

Typically triangulation is the use of more than one method and/or researcher within the same study to counter any gaps that might arise if only one researcher and/or method is used (Denzin, 1989). In the current study, data was collected by the researcher using one method and from one source. Following Flick (2007), in order to reveal and minimise biases, investigator triangulation was used where the researcher and two

supervisors compared their interpretations of interview transcripts. The collective nature of this approach largely confirmed the researcher's analyses and usefully served to extend and at times challenge the emerging analysis. Therefore the use of triangulation acted as an important check on the development of analysis.

2.10 Disseminating Research Findings

Due to the risk of airborne bacterial and viral cross-infection between CF patients, results could not be disseminated to the participants via a group meeting. The researcher sent all participants a results summary (see Appendix 9). Participants were invited to discuss the results with the researcher in person or by telephone or e-mail.

The findings will be presented to the Gene Therapy Consortium clinical research team members and results will also be made available to other Gene Therapy Consortium clinical research teams in the U.K. and to relevant CF health care professionals. The main findings will be submitted for peer reviewed publication.

3 Results

In this chapter, the participants and the duration of the interview period are described. Qualitative findings from the interviews are also presented and these will be considered in further detail in the Discussion chapter.

3.1 Participant Information

Twelve participants took part in the study, seven being male and five being female. The age range was from 19 to 53 years (mean 31.67; SD 10.07). The length of time from Run-in Study Visit One to the interview for this study ranged from 295 to 390 days (mean 347; SD 33.69).

The age at which participants were diagnosed with CF ranged from birth to 48 years (mean 13.83; SD 17.13) with the time since diagnosis to the time of interview ranging from 3 to 38 years (mean 17.83; SD 10.33).

The researcher had supervised access to the participants' Forced Expiratory Volume (FEV1) % predicted scores as recorded in the Run-in Study Visit One. FEV1% predicted is a percentage measurement of the lung function that is expected for someone without CF of the same age, height, weight and gender and is used as a guide to the severity of CF. It was suggested in personal communication with Dr. J. Alastair Innes, lead consultant physician for CF for the Scottish Adult CF Service, that CF severity be ranked in terms of low lung function (moderate range) and high lung function (mild range). No participants were in the severe range of CF, as they did not meet the criteria for the Run-in study.

Of the participants, six were in the mild range of CF and six were in the moderate range. For the former, lung function was within non-CF normal range and their quality of life was largely not affected by CF. For those in the moderate range, there was some impact of CF upon lung function and upon quality of life. There were four participants who had been diagnosed with CF as adults, three of whom were in the mild range and one of whom was in the moderate range. Participant details are presented in Table 1 below.

Table 1: Demographic Characteristics of Participants (N=12)

	N
<u>Gender</u>	
Male	7
Female	5
<u>Age</u>	
19- 29	6
30-39	4
40-49	1
50-59	1
<u>Number of years since diagnosis</u>	
0 – 5	3
6 - 10	0
11 - 19	4
20 - 29	3
30 - 39	2
<u>FEV1% predicted</u>	
Low lung function (moderate range)	
45- 78% predicted	6
High lung function (mild range)	
79 – 120 % predicted	6
<u>Time Between Study Visit One & Interview</u>	
9-10 months	3
10-11 months	2
11-12 months	2
12-13 months	5
<u>Marital Status</u>	
Single	7
Married/with partner	5
<u>Highest Level of Education</u>	
Secondary School	1
Tertiary Education (including those currently studying)	9
Vocational training	2

3.2 Duration of Participation

Each interview was completed within a single visit. The length of interview ranged from 22.1 to 55.5 minutes (mean 32.2; SD 8.6). Interviews three to eleven included participants' thoughts on the interview process. Interviews one and two did not have this recorded (See Section 4.4: Researcher's Reflections on the Interview Process).

3.3 Qualitative Findings

3.3.1 Overview of Participants' Expectations of Gene Therapy

The main aims of the study were to discover the expectations that participants recruited in Scotland and Northern England for the CF Run-in study had of the gene therapy trial and of gene therapy in general. It was also to ascertain whether these expectations changed during their participation in the CF Run-in study. The main aims included whether participants had any misconceptions about gene therapy. Difficulties and benefits of participation in the Run-in study were also explored.

“Expectations” and “Managing Expectations” were the core categories identified through analysis of the participants' interviews. These are detailed through the suggested dynamic relationships between the subcategories “Hoping gene therapy works” and “Strategies for managing expectations” and the major sub-theme “Trusting in the system” (i.e. participants' expectations of gene therapy from the trial and in the future were managed by the use of individual coping strategies and by ongoing trust in the research team and local CF teams). There was an overlap between participants hoping that the treatment would work for them and hoping that it would work for others. The relationship between the core categories and subcategories is illustrated in Figure 3.1 below:

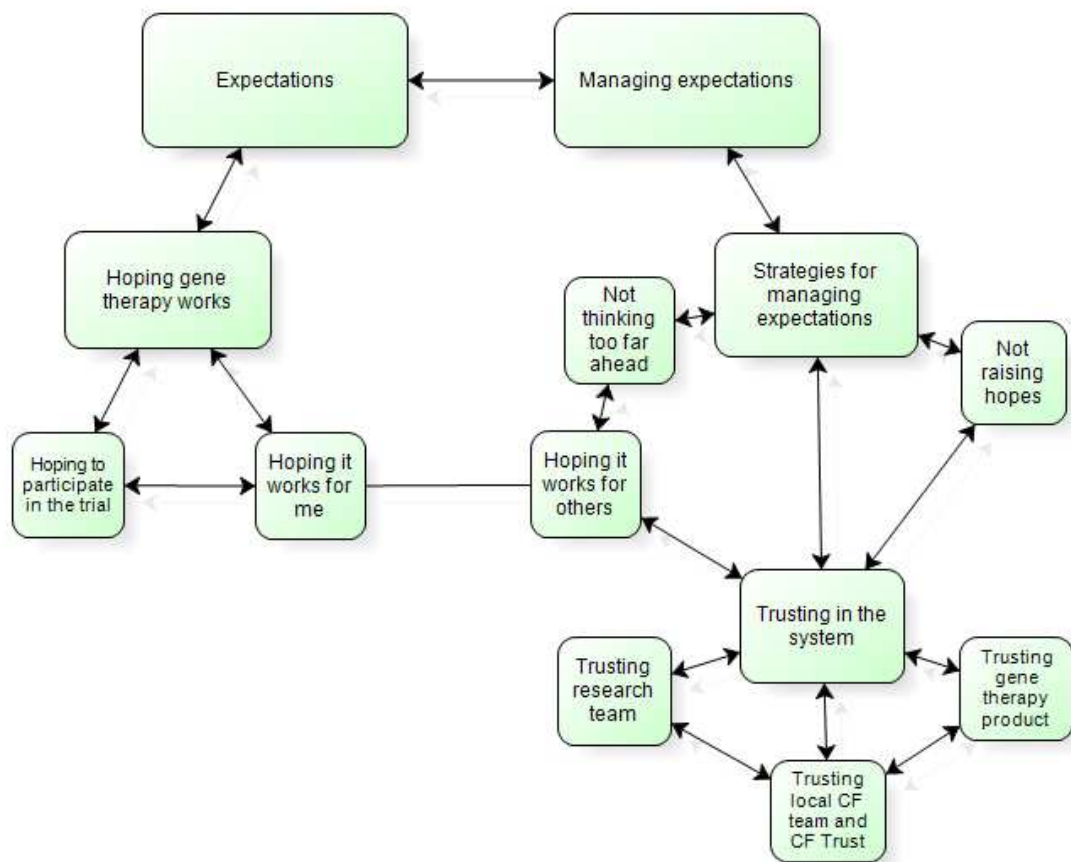


Figure 3.1: Dynamic Relationships between Core Categories and Subcategories

The core categories and subcategories will be discussed in turn, with the sub-categories being described through their respective sub-themes. Each will be supported by quotes from participants' transcripts in order to show the underlying data. Quotes for both researcher and participant are presented in italic font, with the researcher's being in bold font.

3.3.1.1 Core category: Expectations of gene therapy

This category describes the expectations participants have of the gene therapy trial and of gene therapy for CF. The core category “Expectations of gene therapy” is described through the following subcategory and its respective sub-themes:

- Subcategory: Hoping gene therapy treatment works
 - Sub-theme: Hoping gene therapy works for me
 - Sub-theme: Hoping to participate in the trial.

Initial comment on “hope” and “expect”

“Hope” and “expect” were frequently used by participants to describe their expectations of the gene therapy trial. Both of these terms were often used synonymously and therefore could overlap and work in a dynamic relationship with each other. The researcher tried as far as possible to understand what the participant meant in personal usage of these terms, one example being:

So I'd hope, you'd hope but I don't know if you can maybe expect it to be clear cut the first time round.

And what would you say's the difference between hope and expect for you?

You're not wanting to get any worse, you're going to hope that it does work but at the same time you're old enough to realise that things don't always run smoothly. I'm not saying I'd expect it to necessarily work first time but I'd say that's what I mean by I'd hope it would work. (Participant 7, excerpts from lines 238-281).

The main difference between the two terms is that “hope” was used in a much more general sense as an expression of wishing for particular outcomes without assessing the likelihood of how such outcomes could be achieved. “Expect” had a much higher component of realistic assessment of the likely outcome and seemed to apply to more concrete and personal expectation. The researcher considered that for some participants, taking part in the Run-in study moved some “hope” into the category of “expect.”

Therefore by participating in the Run-in Study, participants acknowledged that they were a step closer to hopes becoming expectations. To what extent this happened and whether participants' expectations were realistic will be explored.

Subcategory: Hoping gene therapy treatment works

Of the twelve participants, eight explicitly used the word "hope" in regards to wanting the gene therapy trial to work. The remaining four participants implicitly showed hope of the trial being successful in wishing for clinical benefits from it for themselves, although one mainly hoped for benefits for future generations.

The subcategory "Hoping gene therapy treatment works" is further described through the following components, with analysis being drawn from the researcher's own memos:

- Hoping gene therapy works for me
- Hoping to participate in the trial

Sub-theme: Hoping gene therapy works for me

The researcher found that ten of the twelve participants hoped that the gene therapy trial would have some clinical benefit for them. Four of these participants said that they did not have any expectations or did not know what to expect. The remaining two participants said that they did not expect personal benefit but still expressed the hope that the trial would work for those known to them or those in the future.

Even though the magnitude of clinical benefit anticipated from the gene therapy trial is unknown, there was still a range of personal hopes expressed regarding clinical benefit

from the trial. Based on the researcher's analysis (Memo 43), the hope of personal gain was not always influenced by CF severity. Participants with both mild and moderate CF hoped that medication would be reduced or no longer required. In the two examples below, the first participant in the mild range showed that she would like to be free from all the "little silly things" that go along with CF and the second in the moderate range that she would like to be free from the burden of treatment:

Well, I'm quite healthy anyway so it probably would be all the little silly things that go along with it [CF] like not needing to take Creon [enzyme replacement] anymore or something like that. Being able to kind of to cope, my body to cope with that on its own instead of on medication. (Participant 4, lines 244-250)

a life without having to think, "Oh I've got to rush and go and get the, go home and nebulise [inhale medication] and go and do physio and...", just a bit free with time and life. (Participant 6, lines 457-461)

Whilst it may be that the burden of treatment will be reduced for those in the future, hopes of this from this trial were not likely to be met. In addition, the first participant hoped that gene therapy would remove general symptoms of CF whereas the lungs are the target of gene therapy for CF and likely to remain the only target (J.A. Innes, personal communication, 24 June 2009). This highlighted that participants may not be entirely aware of the intended research aims of gene therapy treatment. In the researcher's analysis (Memo 48), misconceptions seemed less likely to arise when participants moved from hope to expectation, although this process did not seem to have yet happened for the participant in the mild range with hope being in the ascendancy:

Again I suppose I would always hope for something positive to come from it but I don't really know what to expect at the moment. (Participant 4, 189-193)

Regardless of disease severity, participants hoped that lung deterioration would be halted or at least slowed down. A respective example of this from the mild and the moderate range is as follows:

[gene therapy] would kind of keep my lungs in stasis, so as they are now, it would stop the progression of the lungs getting worse and it would just, this would be my level. Which is obviously fantastic... (Participant 8, lines 15-20)

It'll be a great help for everybody with CF, keep you sort of steady at the same level. You hope you won't get any worse. (Participant 7, lines 17-20).

The researcher considered whether the participants' experience of peers in the CF community becoming progressively worse or dying was influencing their expectations of personal benefit from the trial. It was unclear whether the first participant knew that current lung function is the best predictor of future health (J.A. Innes, personal communication, 24 June 2009), but it was clear that with lung function in the normal range she still hoped that gene therapy treatment could deliver guaranteed lung stability. Whilst this was an understandable hope, it was unlikely to be the outcome of the immediate gene therapy trial since it is largely designed to measure clinical benefit.

However, misconceptions could also be recognised and challenged. The participant herself corrected her own understanding by bringing it to a more realistic level. She anticipated that a successful outcome would take at least ten years and asked whether she would be well enough to benefit from treatment at that time. Yet she was still able to hope for immediate benefit for herself, demonstrating how a participant's optimism can exist alongside realistic appraisals.

Indeed, the researcher's analysis indicated that hope was not always tempered by external reality (Memo 2). When participant knowledge of the success and limits of gene therapy in general was evident, this did not necessarily preclude hope that the symptoms of CF and their consequences would be removed. One participant in the mild range had read the Run-in patient information sheet and had some knowledge of the uncertainty of human trials, yet still wished for the following:

[the success of the gene therapy trial would] just mean that I can lead an active normal life without having that nagging doubt in the back of your head all the time, "What if?" [getting an infection and lungs deteriorating significantly] (Participant 12, lines 424-427)

This level of hope was similar to that of a participant in the moderate range who had a self-confessed lack of knowledge of the Run-in study and of gene therapy in general:

I just wouldn't have that cloud over my head saying I've got CF all the time. I'd just be free. (Participant 5, lines 502-504)

This raised the question as to how hope and expectation worked together in a dynamic relationship since hope was present regardless of level of knowledge. The hope expressed by the first participant did not seem to be tempered by his awareness that the multi-dose gene therapy may not work first time round:

If I was selected, again the outcome of the trial... there's what I'd like to happen obviously which is it works, on your current treatment for the rest of your life, happy days. I think it's really hard to have any expectations until as I said you know roughly what's going to happen with it. (Participant 12, lines 365-372)

It would appear that participants could be well informed and yet choose to hope rather than expect more realistic outcomes from the trial.

Sub-theme: Hoping to participate in the trial

In this sub-theme, the hope of participation is in a dynamic relationship with the hope of receiving active treatment and the level of expectation of potential benefit from the trial.

Overall, eleven out of twelve participants explicitly expressed the hope of being selected to participate in the gene therapy trial. This consisted of all six participants in the moderate range and five participants in the mild range. Although willing to participate, the remaining participant who had been diagnosed with CF as an adult did not expect to be selected based on the Run-in criteria because he believed himself too healthy for the gene therapy dose:

They wouldn't see much of an improvement by giving me gene therapy (Participant 2, lines 376-377).

Of the participants, all six in the moderate range expressed the hope of being selected for active treatment on the gene therapy trial, although they were also willing to be controls. With participants in the mild range, three out of five explicitly hoped for active treatment, with two implicitly indicating this. As above, the remaining participant was willing to have active treatment but did not expect it. However, he along with four other participants in the mild range explicitly said they were willing to be in the control condition. Only one participant in the mild range, who was diagnosed late with CF, said he would be “a bit disappointed” not to be receiving active treatment albeit he recognised the placebo was necessary to the trial (*Participant 1, line 502*).

The researcher's analysis (Memos 9 & 38) of the difference in hope and expectation between the two participants above with late diagnosis indicated that the extent to

which a person had adjusted to having CF may have influenced their approach to the trial. Participant 2 who was also in the mild range had had over ten years to adjust to diagnosis whereas Participant 1 was still coming to terms with his diagnosis as it was “rather fresh and actually rather raw” (line 446). Further, Participant 2 described less CF symptoms than Participant 1 and appeared to have less personal investment in participating in the trial, his main motivation being to help a family member with moderate CF.

Participant 1’s potential sense of disappointment about the possibility of not being given active treatment was also expressed by other participants:

I think it’s a great thing like when I first heard about it, it was like, I can’t believe it! It’s [going to] be so good. I’ll probably be disappointed about not being able to be part of that. (Participant 4, lines 323-327)

I’d probably be a bit disappointed if I wasn’t involved in the actual gene therapies part of it... it would be a shame to get to that point, which is kind of make or break and I wasn’t chosen to be part of the next part of it because it’s been interesting you know. (Participant 11, lines 296-303)

Whilst the possibility of not being selected for active treatment was anticipated, with one participant predicting that it would be “devastating” (Participant 4, line 524), there was evidence that she had not anticipated this in any detail (Memo 1). During the interview, the same participant actively thought through the process of how she was likely to experience being disappointed, imagining it as a short-term experience:

I’d probably think about it quite a lot, but really the same as everything else, you start to think about it less as the days go on. It’ll probably be okay I think. So I’ll say that now though. I don’t know. (Participant 4, lines 334-339)

This response showed the similar difficulty of accurately predicting a response to not being selected for the trial itself as opposed to being selected for the active treatment.

Indeed the participant indicated that she was thinking about selection “quite a lot” (*line 343*).

This raised the question of how participants would adjust to not being selected for the gene therapy trial. Whilst there was not sufficient evidence to suggest that there would be difficulties for every participant if not selected, there was a sense of the unknown in how participants would react, and a strong sense of hopes potentially being dashed if the trial were not successful.

Despite participants actively managing expectations of the trial, several participants had invested significant hope in the trial. As described by one participant, this was perhaps because there was the “chance that it would work” (*Participant 7, line 316*). Indeed, one participant who had recently received a letter informing her of a delay to the gene therapy trial became so upset at the thought of not being potentially well enough for eventual selection that the interview had to be prematurely closed. In the researcher’s analysis (Memo 48), this participant was one of two who appeared anxious to benefit from active treatment on the trial. As one was in the mild and one was in the moderate range, anxiety was not indicative of disease severity. However, both had been diagnosed as adults with CF within the past five years and, as indicated above, there may still have been adjustment to the implications of having a diagnosis of CF.

3.3.1.2 Core Category: Managing Expectations

This category describes not only the expectations participants have of the gene therapy trial and gene therapy in the future but also the strategies they are utilising to be able to manage and continuously refine these expectations. This is particularly relevant

because at the current time, not only is the participants' selection and thus participation in the gene therapy trial unknown, but the actual outcome of the gene therapy treatment for people with CF is unclear.

The core category "Managing expectations" is described through the following subcategory and its respective sub-themes:

- **Subcategory: Strategies for managing expectations**

- Sub-theme: Not raising hopes
- Sub-theme: Not thinking too far ahead
- Sub-theme: Trusting in the system
 - Trusting the gene therapy product
 - Trusting the research team and the information they provide
 - Trusting local CF teams and the CF Trust
- Sub-theme: Hoping gene therapy works for others in the future

Subcategory: Strategies for Managing Expectations

Sub-theme: Not raising hopes

Not raising hopes was a strategy that five participants used to safeguard themselves against being disappointed if the trial proved not to be clinically successful (Memo 39). For example, one participant was expecting there to be challenges in the development of a gene therapy product:

There's always a bit of trial and error and so obviously you'd hope that it would work, but maybe part of me at the same time expects it probably wouldn't first time round or maybe not as so smoothly next time. (Participant 7, lines 228-234)

Participants were also using a thinking style conducive to keeping hopes in check. As

reflected in one of the researcher's memos (Memo 31), one participant demonstrated how she was actively avoiding thoughts of a successful clinical outcome from the trial, preferring this to come instead as a "great surprise" (*Participant 11, lines 148-149*). Hopes were implicit, perhaps even for the participant, with her wanting to hope but controlling the hope in order to avoid disappointment. This possibly stemmed from her realistic expectations of the trial:

I don't expect it to make much of a difference to me as I don't think it will be in my lifetime that it'll cure or anything like that. (Participant 11, 115-118).

Another participant was deliberately not thinking about the Run-in but going about his everyday life as usual:

I'm not getting my hopes up, just take it as it comes.

So how much are you thinking about it in-between times?

I'm not thinking about it. Just going in and doing the tests and that's it.I just get on with my life and just that's it, just take each day as it comes. (Participant 10, lines 281-296)

In addition, the researcher's analysis (Memo 39) indicated that participants used specific criteria whereby they could avoid raising their hopes until they could be more certain of a positive outcome. To illustrate this, one participant realised that she could ask for further information about the gene therapy trial before it started but was reluctant to do so. Her response implied her assumption that the information given would be positive therefore asking might engender false hope:

So what would happen if you asked for information now, compared to waiting till later?

I suppose I could really, but I wouldn't like to get my hopes up and get all excited and then find out maybe it doesn't, there isn't enough money, maybe it's not going to be continued. (Participant 6, lines 166-173)

This was in contrast to Participant 12 (See Sub-category: Hoping gene therapy works for me), who eagerly sought information. Regardless of whether participants sought or avoided information, they still seemed to value hope as a coping mechanism.

Sub-theme: Not thinking too far ahead

There was evidence of four participants using the strategy of not thinking too far ahead in order to keep expectations realistic. A participant in the high lung function range set the criterion of “wait and see” to regulate expectations, saying his expectations of gene therapy would change if there were a viable gene therapy product available:

If there's something in front of me and it works, great. If there isn't, well there isn't, it's not there. You know, what's the point in getting upset about it? (Participant 12, lines 733-737)

However, one participant in the low lung function range went even further in not allowing himself to expect that gene therapy treatment would work until he had first seen proof of this:

My views will probably change once the gene therapy does come in and helps everybody and I'll probably see things different but up until then I'll just see the way I see things. (Participant 10, lines 88-92)

In the researcher's analysis (Memo 41), some participants experienced the process of managing expectations within the personal context of living life for now and not dwelling on the future possibility of gene therapy. This was shown in the following example of a participant who realistically explained that he might not be selected for the gene therapy trial, and indeed had not considered if the active treatment would be successful:

I don't really tend to consider it much. ... I'd rather just keep on living instead to the

full just now, just cross the bridge when it comes to it. (Participant 7, lines 731-736)

It is common for people with CF to live life to the full without thinking of the future ramifications of the disease and the researcher wondered whether this influenced the reluctance to think about the possibilities of benefit from gene therapy treatment. It was likely that the participant was managing the uncertainty of the outcome of the trial in the same way as he managed the uncertainty of whether his lung function would remain stable i.e. by not thinking too far ahead.

However, a contrasting example was shown in the approach of one participant who had inadvertently believed that he was being offered gene therapy treatment immediately. Perhaps because he had been in a position when he had believed the trial to be imminent, he was able to think ahead to its eventuality in the hope that it would make him physically “better, fitter and healthier” (*Participant 1, line 48*). Within this process, he too was aware that he might not be accepted for the trial and therefore qualified his future expectations:

I try to keep people’s expectations realistic. I try to keep my own realistic. (Participant 1, lines 53-55)

Although the participant did not express how he was trying to keep the expectations of others realistic, he stated for himself that he would grasp “with both hands” (*line 275*) the opportunity even to be two percent better due to receiving active treatment. The researcher considered that there was some evidence of the tension between thinking of the future clinical benefits of the trial and yet trying to keep his expectations realistic (Memo 2).

Sub-theme: Trusting in the system

The issue of patient trust in the medical system is crucial. Without trust, patients find it harder to work with clinical teams to maximise medical care and to manage and, at times, adjust their expectations of their disease. This sub-theme explores the important question of when and how participants in the trial used trust in the medical and wider CF system to manage their expectations. The following three aspects are considered within this sub-theme:

- Trusting the gene therapy product
- Trusting the research team and the information they provide
- Trusting local CF teams and the CF Trust

Trusting the gene therapy product

Participants' trust in the gene therapy product increased as a result of the growing realisation that an important national study was taking place. This was reinforced after the required visit to Southampton for a three-dimensional lung scan as part of the Run-in study. Nine participants appreciated the visit with three not mentioning the benefits of it. The researcher's memo (33) indicated that because of the visit to Southampton, participants became aware of the researchers doing something bigger and more real than they had first thought. One participant summed this up succinctly:

I think I feel more positive about it. I think beforehand it seemed a little bit sci-fi... And I think now it feels a bit more real. (Participant 3, lines 529-533)

Indeed, over the course of the Run-in study six participants saw their expectations of gene therapy increasing, three being in the mild and moderate range respectively. This increase was because the Run-in study was already happening, making it easier to

expect that gene therapy treatment would now be developed and become an even more effective treatment in the future.

In the context of people with CF having lived with the hope of gene therapy treatment for two decades, one participant in the mild range indicated that the period of waiting was now drawing to a close. She moved from a position of frustrated hope:

Is it really going happen, we've been talking about this for such a long time? (Participant 8, 949-951)

to an expectation that an effective product was now going to be developed, though having recently attended lectures on gene therapy she expected that it would not be for five to ten years:

It is within our grasp. That they are starting to do like single dose trials, and just with having the Run-in study take place it's like that, "Okay, you know we're off the starting block. (Participant 8, 955-960)

The three participants in the moderate range also saw gene therapy treatment as something much more possible, examples of this being:

[Expectations are] much higher...Just because I didn't know they were doing it back then and now I know what they're trying to do. (Participant 5, lines 483-488)

It's just more real..... I'd just always heard about it and talked about it and read about it that this is actually happening. (Participant 6, lines 483-486)

Given that six Run-in participants' expectations of the gene therapy product had increased even without participating on the gene therapy trial, the researcher considered that expectations would be higher when participants were in a position to potentially be receiving active treatment on the trial (Memo 46).

Of the six participants who had seen no change in expectation, one participant from the mild and one from the moderate range respectively said that this was because there had been no increase in their knowledge. One participant each from both ranges said that they had had no expectations to begin with and had not developed any over the course of the Run-in. However, throughout the Run-in, one of these participants anticipated that participation in the trial could be something “very big” (*line 88, Participant 11*) if it were successful and became more eager to participate because of its importance. One participant from each range required to see the finished product in action in order to amend their expectations as to its effectiveness.

Although two participants had the benefit of a scientific background in understanding gene therapy in general, no participant expressed confidence in fully understanding the gene therapy treatment in the forthcoming trial. The overall level of knowledge indicated that participants were less likely to understand the gene therapy product. Despite this, twelve participants were willing to receive active treatment though with the following different perspectives.

There was evidence of participants not seeing the need to understand the science behind the gene therapy product in order to have faith in it, thereby trusting the research system that had developed it and being confident in their expectations of it being safe enough to use:

To be perfectly honest I don't even know how the drugs I'm on work so assuming that they work. I'm not really going to be so bothered about the whats, the whys, and ifs and hows in particular... (Participant 1, lines 35-40)

Yet one participant appreciated that concern about a gene therapy trial was warranted.

She based her confidence in the product on reasoning that the gene therapy product would be safe enough to use by the time of the gene therapy trial, expecting that it would have previously been tested on others in the single dose safety trial:

I suppose with any medical trial you have to be nervous about taking something into your body that hasn't been, you know, has only been tried on a few people and whether it will have any really bad effects, but I think I'd be reasonably confident that it had been tested enough that it wasn't going to do me any harm. (Participant 3, lines 173-180)

Four other participants expected a stage-based development of the product, one of whom anticipated that the gene therapy product might not initially work:

You know, it might happen that nothing, it actually doesn't work given that they're human trials. Back to the drawing board for them sort of thing. (Participant 12, lines 372-374)

However, he anticipated that it would be a viable product and therefore worthy of trust, expressing the hope that it might be ready relatively soon:

It might be a human trial in ten years but it's been done in mice and proved successful and saying, "Now it's like we're actually doing it humans now" so it might be in your very near future. (Participant 12, lines 782-787)

The researcher's analysis (Memo 15) suggested that this participant's citing of the previous success of gene therapy for CF in mice made the gene therapy product for humans seem more likely, even though it has proved difficult to replicate the disease in the lungs of animals. Therefore it is likely that there was a leap of faith in the belief that the product would be in the "very near future" and this is perhaps why the participant spoke of this in tentative terms by using "might." However, this may also have been a strategy to prevent hopes being raised.

Another participant described the development of a “safe” product, which would then be superseded by a more effective treatment:

And then the second lot of research that will kind of continue on after that [the “safe” product], will be the big “Wow.” You know, you maybe only have to take it very, very occasionally, and it will be amazing. (Participant 8, lines 117-121)

The participant appeared to trust that the “safe product” would indeed be safe. Despite being well informed of the trial to date, she offered no description of the risks that could be involved in a potentially dangerous procedure. The researcher wondered whether this indicated the level of trust the participant had in the research team such that she was able to expect a safe product.

Trusting the research team and the information they provide.

Trust in the research team was demonstrated with regard to many areas of their work, which included trust in the selection criteria for the trial, overall trust in the trial and trust in the information provided by the research team.

Participant’s trust in the research team using expert criteria for selecting participants for the gene therapy trial was exemplified in the following statement by a participant in the moderate range:

If you don’t meet the criteria then you obviously can’t be selected. It’s not something you can go and cry about. It’s just they’re the experts. They know what they’re looking for. (Participant 7, lines 758-762)

This trust in the selection process applied not only for the Run-in Study but also for the main gene therapy trial. Whilst not being selected would be disappointing, the above participant’s trust was such that he expected the research team would make the right decision, thereby removing any sense of personal responsibility for him to be as ready

as possible in order to be selected (Memo 29). This contrasted with another participant in the moderate range who took on the responsibility to stay as fit as possible in order to be selected:

I just need to get healthy, stay healthy, when I come back, do very good and hopefully they choose me. (Participant 5, 423-425)

One factor that seemed to help participants to trust the research team was a belief in the skill of team members and their approach towards the research. For example, one participant commented that the research team was professional and that this had enhanced her trust in them:

They're clearly very professional and I'm sure they're extremely good at their jobs (Participant 3, 498-450)

However, the same participant had initially wondered about the seriousness of the research team due to the adoption of a casual approach. This seemed to indicate that trust in the research team was a developing process (Memo 47).

The trust that participants had in the research team was also illustrated by the fact that they felt that the research team would continue to undertake research even beyond their participation. This would help others known to the participants. For example, a participant in the mild range was taking part for the future benefit of a family member but whilst not personally investing in the outcome of the trial, trust was still required in the research team to make the best use of his contribution to the research effort:

My contribution is a little cog in a big machine, you know that the actual system is taking care of my contributions without me having to personally have to do too much. (Participant 2, lines 506-510)

Only two participants had sought information about the gene therapy trial from the research team. Three of the remaining ten participants expressed confidence in the team being able to deal well with their enquiries, two examples of this being:

I'm sure they [research team] would clarify it more like if I was selected, actually let me know what was going to happen, it's just not really been talked about really yet. (Participant 4, lines 186-189)

I'm sure if I discussed it with any of the team I'm sure they'd be happy to talk until the cows come home about it, but I never have. (Participant 3, lines 44-46)

The latter also indicated that she would believe implicitly in any information from the research team:

I think anything that came from the team in writing or them telling me it I would believe it just automatically. (Participant 3, lines 54-57)

Of the seven participants who had not sought any information about the gene therapy trial, five did not feel the need to do so. The reasons given were various. One participant said that he was not the sort of person to ask for information, one was more interested in asking questions on current health status and one cited general knowledge about gene therapy from media sources. Another participant was contributing to research for the benefit of others and one said she had enough knowledge about gene therapy but felt that there had not been clear communication about the Run-in study, albeit she had not asked any questions of the research team.

In contrast, the two remaining participants were planning to ask the research team for information, one wishing to wait until selection for the gene therapy trial and one having recognised during the interview for the current study that he should ask for information as he did not know anything about the trial. The researcher's analysis

(Memo 6) indicated that for this participant, and for one of those who did not feel the need to ask for information, respective parents had actively been obtaining information about gene therapy albeit not about the trial itself. It was likely that in these cases, not asking for information did not indicate lack of trust in the team but continued trust in parental support, which is a frequent feature of young adults with CF.

There was also evidence of two participants believing information from the medical research fellows in the research team because of their privileged position regarding knowledge. Whilst one participant appreciated the frank approach of the doctors, the other participant felt that his questions asking for specific outcomes of the trial could not be answered:

The doctors should know more than anyone else so I prefer to talk to them and believe the information that they tell me and the doctors are very forthcoming with information and they don't try and make it all flowery and rosy or anything like that. (Participant 9, lines 38-46)

They might not be the right questions [he has asked the research team] to be honest with you. There's just nothing clear about what's going to be the future after the gene Run-in. (Participant 12, lines 307-310)

The comments of the second participant drew attention to the fact that this type of research cannot be trialled in animals since it is a human disease which has not yet been fully replicated in animals. Yet the participant still commented that information from the research team was “not freely given out” (lines 314-315).

It was possible that the second participant above may not have had full trust in the research team's communication with him, resulting in him feeling less supported in managing his expectations since he did not receive answers that would have been of help. However, he concluded that lack of information was perhaps “just cos we don't

know” (lines 317-318), recognising the uncertainty of human trials such as this one. The researcher’s analysis indicated that two separate but linked processes were happening: the research team itself could not guarantee the outcome and the participant was experiencing the uncertainty of not knowing the personal outcome of the trial and of not having this uncertainty addressed (Memo 7).

Participants felt that the research team were generally interested in their ongoing research care and were friendly. Evidence of this was being given clinical benefits such as medical advice and being helped with symptom management. There were four participants who experienced clinical benefits, two of whom had been diagnosed in adulthood. An example of experiencing benefits is as follows:

I’m aware that I’m in probably better shape now and I know that I’m perhaps sort of stable between visits so the gene therapy Run-in study just gives me a bit of back up. (Participant 1, lines 138-142)

Trusting local CF teams and the CF Trust

Five out of the twelve participants showed evidence of trust in their local CF teams during their participation in the Run-in study (Memo 17). The advice of a medical consultant was called upon when one participant in the mild range expressed the following disappointment about not being able to keep receiving the gene therapy product if the trial were successful:

If you do get taken to take part in the gene therapy study, and you feel better for it after a year, and then you come off it again. You don’t want to not be in it, but on the other hand, to know what’s going to be great, and then not have it after that, go back to normal life, but, however, however. (Participant 8, lines 151-159)

The participant felt reassured by her medical consultant saying that the trial would be more about tracking changes than about giving clinical benefit. The participant's sense of reassurance indicated that trust could be maintained in clinical teams responsible for participants' ongoing physical care despite any potential disappointment.

A further example is one participant in the moderate range who revealed that he had trusted the doctors from the local CF team to initially provide the information he needed about the Run-in study:

Well I didn't really know a great deal about it. I'd just sort of been, find out from the doctors at the CF clinic. (Participant 9, lines 286-287)

This suggested that knowledge of the gene therapy research was important for the local CF team in helping it to facilitate participants' experience of the trial.

Participants trusted in sources of information in addition to the research team and local CF team. Half of the participants trusted the information from the CF Trust regarding the gene therapy trial, one showing that she found information from the research team and the CF Trust the most believable:

The information from [the doctors and the CF Trust] are the things to believe in, straight from the horse's mouth rather than circumstantial evidence. (Participant 8, lines 63-67)

In contrast, one participant with a late diagnosis showed belief in the information from the research team and from the CF Trust but only in written form. Whilst she appeared to trust both sources of information, the requirement of needing statements committed to paper indicated that there was some level of mistrust as well as trust, which may have reflected the participant's anxiety. This need for confirmation helped her to

manage her expectations regarding the gene therapy trial, thereby helping her to cope with the uncertainty regarding the outcome (Memo 32):

When there's a report sent [from the research team] saying this is what is going to happen, and this is the result, then I'll believe it.... if I read it on the forum that the CF Trust have put it on [update on trial], then I mean they would never say anything if it hadn't happened. (Participant 6, lines 215-218; lines 238-241)

Sub-theme: Hoping gene therapy works for others in the future

In this sub-theme, participants were trusting that there would be an eventual, successful clinical benefit from either this trial or a future trial for other people with CF. By hoping for this benefit for others, participants showed altruism but also used hope as a way of being able to think ahead more comfortably i.e. without as much personal investment. In this way, hope and expectation worked dynamically since hope seemed to be more unreservedly expressed than when thinking of personal benefit and participants seemed to have a greater expectation of future success for gene therapy than of the imminent gene therapy trial.

Analysis of the data (Memo 44) indicated that there was overlap between hoping for benefit for oneself in the future and hoping for the eventual benefit of others, one example being:

So, you know that's quite cool [helping a known child with CF]... and of course it might help me in the long run as well. Who knows? (Participant 3, lines 111-119)

The researcher speculated that the hope of potential benefits from gene therapy treatment in “the long run” was a way of managing expectations by allowing for hope to continue beyond participation in the trial. This would be even more so if treatment outcomes of the imminent trial did not meet expectations, thereby helping participants

to have a strategy for dealing with disappointment. It was not always clear whose future was referred to in terms of receiving clinical benefit:

[being chosen for active treatment] you would actually feel that there was a benefit and it would give you hope for the future that the product's actually working. (Participant 8, lines 213-216)

In the researcher's memo (Memo 31), the role of altruism was explored and whilst it was present in seven accounts, only one of these participants expressed no hope or expectation of personal benefit. Another of these participants' accounts demonstrated how participation may initially have begun with altruism being prominent but that another reason for participation may have emerged as selection for the gene therapy trial drew nearer:

It maybe moves onto a slightly more personal level from a kind of, "This might help everyone with CF" to a, "Hang on, you know, it might help me" [laughter]. (Participant 12, lines 815-818)

Although there was evidence from the data that all twelve participants were hoping that gene therapy treatment would benefit others with CF, only one highlighted that emotional maturity was required to be able to really do so:

It will help generations in the future and I think it depends on your emotional confidence whether you can be glad for the benefit to others, or whether you're still focussing on "It's not going to do me any good". (Participant 8, lines 111-1116)

The same participant was managing awareness of potential personal loss based on the shortfall between previous expectations of gene therapy treatment and current reality:

A lot of that PR spin that was about, you know, it's like, "Let's raise money to find a cure for CF" has really fallen away in the past five years to go to, "It's an improved treatment" because people were so clinging on to the idea of gene therapy being so wonderful and it's really not. (Participant 8, lines 79-86)

This highlights that wider expectations of gene therapy beyond the current trial were not without complexity since being able to hope for future benefit for others required some level of acceptance that the gene therapy product was not likely to be as effective for current participants. Indeed, maximum benefit was expected for children and those not yet born:

I presume for children it'll make a huge difference. They won't have the lung damage. I presume for them that's what is going to be the most important thing. (Participant 6, lines 58-62)

For the new generation coming in, fantastic. They're not even going to know CF as anything serious. (Participant 8, lines 95-98)

The researcher's analysis (Memo 45) indicated that six participants expected a "huge" or a "massive" difference for those in the future e.g. not having a life-threatening illness, greater longevity, reduced medication and not having lung damage.

Of the twelve participants, six expressed the hope of a future cure for CF, two of these combining expectation and hope in their responses. In the following example, the researcher considered that the participant was aware of the difference between hoping for a cure, which would happen in an ideal world, and expecting a cure, which would be based on the reality of research (Memo 23). Continuing research would bring that reality closer:

I'm not particularly expecting that in a year's time there'll be a cure, but, you know, obviously in an ideal world there would be. But, I think that all I would expect is that in a year's time they'll be closer. (Participant 3, lines 191-195)

The remaining six participants hoped that gene therapy would potentially be a partial cure or an improved treatment. This is demonstrated by the participant below who expected the possibility of an improved treatment to keep the lungs stable. However, it

was unclear whether she was conflating her expectations with those she anticipated for the research team (Memo 35):

I mean it may take a long time, longer than expected, but they're still doing it. It's not just in the planning stage or the thinking through stage, it is happening. (Participant 6, 494-497)

It may be that hopes for others in the future could be more safely managed, as exemplified in the following:

If, you know, people have said, "How do you feel about it?" you know, I've always just had the mindset that it's nice to know I'm part of a research for generations to come and not for me. (Participant 11, lines 206-210)

Even though it won't affect me, it will help the other CF patients and then from that they'll keep on, getting closer to finding stuff about CF but not probably give it to us but to all other CF patients. (Participant 5, lines 348-355)

However, given the scientific rationale for the gene therapy trial, participants were realistic in terms of thinking of the likelihood of there being much greater benefit for children and for those not yet born than for themselves. Nevertheless, one participant still allowed himself to hope for personal benefit whilst remaining realistic:

I'm quite realistic about [the gene therapy trial], I'm not expecting it to be the wonder cure type thing. But I'm hoping it is! (Participant 9, lines 177-181).

4 DISCUSSION

The findings of the current study are discussed in this chapter in comparison with previous research. Suggestions for future research are also made. The chapter considers strengths and limitations of the current study, includes some reflections from the researcher and assesses the contribution made by the findings.

4.1 Qualitative Findings

4.1.1 Core Category: Expectations of Gene Therapy

Subcategory: Hoping gene therapy works for me

The researcher found that ten of the twelve participants hoped that the gene therapy trial would have some clinical benefit for them. Participants from the current study hoped to benefit in a similar way to respondents in the survey by Duff (personal communication, 17 June 2009), albeit the latter were not participating or scheduled to participate in a gene therapy trial. Participants in both studies expressed the wish for reduced intravenous antibiotics and less chest infections. They also hoped that lung deterioration would slow down. The similarity of findings in both samples indicates that hopes of positive outcomes from gene therapy treatment are likely to be present before participation begins in gene therapy trials. The strength of hope increased for half the participants in the current study as they underwent the Run-in study (See Sub-theme: Trusting in the system). As current findings have indicated, hopes of gene therapy being an effective treatment can increase by participating in a pre-treatment phase of a gene therapy trial.

This was in contrast to the findings by Blair *et al.* (1998, p.220) that “most patients” had a realistic understanding that they should not expect any personal clinical benefit from participating in the safety trial. One reason for this difference may be the awareness of participants in the current study that multiple doses of the gene therapy product could produce clinical benefit, although the magnitude of this remains unknown.

The levels of optimism for personal benefit from the current trial were higher than those in the Blair *et al.* (1998) study in which nine out of sixteen patients were “hopeful or very hopeful” of personal benefit from gene therapy (Blair *et al.*, 1998, p. 219). This may reflect a higher level of optimism regarding gene therapy treatment after eleven further years of research progress and the prospect of a novel multi-dose gene therapy trial. Perhaps a similar level of expectation is reflected in Duff’s findings (personal communication, 17 June 2009) because it is based on sample opinions taken recently of CF patients. A high level of expectation of gene therapy was shown with 83.2% of 266 respondents being convinced that gene therapy would be a treatment within ten years. It was unclear what criteria respondents were basing their response on.

However, some of the positive expectations in the current study are unlikely to be met by the gene therapy trial e.g. having CF symptoms removed completely, no longer requiring medication. Whilst it is difficult to evaluate these expectations, it is more realistic to expect that an effective product will take time to develop based on the difficulties to date in developing gene therapy for CF. Only two participants in the current study gave a clear time-frame for improved treatment, the first positing that it would take at least ten years and the second between one to two years.

There is evidence to suggest that hope may be stronger than expectation in participants undergoing participation in trials. High levels of optimism about clinical outcome are present in extant literature. Despite the chance of clinical benefit in oncology phase one clinical trials being less than 5% (e.g. Daugherty *et al.*, 2000; Decoster *et al.*, 1990; Hoff *et al.*, 1991), vulnerable participants may have greater difficulty in distinguishing between the research and clinical aspects of a clinical trial (Daugherty *et al.*, 2000). For example, in a survey interview study of 144 advanced cancer patients, 90% of people interviewed believed that they would experience clinical benefit as a result of active treatment despite having been informed of the low likelihood. In the current study, the magnitude of clinical benefit has been made less explicit and therefore may appear more possible. However, this does not explain the lower percentage (83%) of current participants actively hoping for clinical benefit than those (90%) in the study by Daugherty *et al.* (2000). Yet the latter had a larger sample size, and patient populations were different therefore comparisons must remain tentative.

Altruism was a motivating factor for seven participants in the current study. Participants in other trials have also reported the motivation to be altruistic, which may be due to identifying with future generations who will have the same condition. This sense of altruism is captured in the Blair *et al.* (1998) study, where it was reported as the main motivation for the majority of participants. Altruism has been found as a motivation for participating in randomised clinical cancer trials (Jenkins & Fallowfield, 2000). There is also evidence from a study on participation in HIV trials that the motivation for participating is for the potential future benefit for others, rather than necessarily for anticipated personal benefit (Wendler *et al.*, 2003).

However, only one of the seven participants in the current study who demonstrated altruism expressed no hope or expectation for personal benefit. This is similar to the finding that the motivation for trial participation is the hope of treatment having both personal benefit and benefit for others (Penman *et al.*, 1984; Slevin *et al.*, 1995).

Hoping to participate in the trial

Eleven out of twelve participants explicitly hoped to be selected for the gene therapy trial, nine of whom explicitly wished for active treatment and two of whom implicitly indicated this. Eleven participants explicitly said they were willing to be in the placebo condition. The overall level of willingness to participate corresponds to qualitative data that shows that interest in participation in gene therapy trials is currently high. Respondents in the multi-survey study requested information on the progress of clinical trials and on how to become trial participants (A., personal communication, 17 June 2009).

Even if participants in the current study are not selected for the gene therapy trial, there is some evidence that rejection may not deter future participation. One participant in the current study said that he would try to be selected for another Run-in study, with hopes of selection for a future gene therapy trial. He remained optimistic about “just expecting something good out of it all” (*Participant 5, line 489*). In the study by Blair *et al.* (1998), three participants were not deterred from any future involvement despite being excluded from the gene therapy trial. They were marginally less optimistic about the potential for gene therapy for CF than those who had participated in the trial. Whilst this finding is tentative in both studies, it suggests that optimism about future

involvement in trials remains undiminished by not previously having been eligible for participation.

4.1.2 Core Category: Managing Expectations

Subcategory: Strategies for managing expectations

The current study indicated that participants on the Run-in study were employing a range of strategies to manage their expectations regarding an effective clinical outcome of the gene therapy trial. It was found that five participants were not raising their hopes about the outcome and four participants were not thinking too far ahead. It has been argued that the use of avoidance strategies has some benefit for short-term situations and there is some evidence to suggest that such strategies are adaptive when patients with CF are faced with a situation that is not able to be controlled (Abbott, 2003). It therefore may be that the strategies of not thinking ahead and of not raising hopes are adaptive when faced with the difficulty of not being able to predict selection for the gene therapy trial.

In terms of possible continuing participation into the gene therapy trial, there is evidence that active coping strategies are more effective for long-term situations (Abbott, 2003). However, these strategies work best for situations that are controllable. It is therefore not clear how the participants in the current study who use avoidance strategies to manage their expectations will continue to benefit if their participation is continued into the gene therapy trial.

Yet the findings on coping strategies are not conclusive. Whilst there is evidence that different coping strategies may be used within chronic illness (Macdonald, 2006),

Abbott (2003) posits that it is more important to consider what is of most help for psychological functioning rather than strategies being adaptive or otherwise. The majority of participants on the current study had not experienced psychological difficulties during participation and indeed four had actively benefited from the experience through receiving clinical support. Therefore strategies to manage expectations were largely effective. Abbott (2003) suggests being aware of the match between expectation and outcome and of evaluating how strategies are working for individuals. It may be that the strategies of the participants will change over time (e.g. Lazarus & Folkman, 1984).

In an earlier study of expectations of gene therapy, only one out of sixteen patients on a single dose safety trial used the strategy of not thinking about gene therapy too much in case anxiety about it increased (Blair *et al.*, 1998). This was in the context of managing associated anxieties about gene therapy treatment rather than managing positive expectations of it. Indeed in Blair *et al.* (1998), there was a significant minority of patients who had anxiety disorders, being more likely to be worried about the safety and potential of gene therapy treatment. The two patients in the current study who were anxious were concerned about missing the potential of the active treatment but were not worried about the safety aspect of treatment. However, this highlights the importance of eliciting feelings and opinions of participants on trials to gain valuable information about how trials are progressing and indeed being experienced (e.g. Griesenbach & Boyd, 2005).

4.1.3 Sub-theme: Trusting in the system

Trusting the gene therapy product

In the current study, participants' trust in the gene therapy product grew as they became aware of the researchers doing something bigger and more real than they had first thought. There was evidence of six participants who had seen an increased expectation of gene therapy being an effective treatment, one having confidence in the product being developed safely for use. Optimism among Blair *et al.* (1998)'s sample for an effective gene therapy treatment in the future was also high. Whilst an increasing sense of optimism about gene therapy was reported by a third of 266 respondents in Duff's study (A. Duff, personal communication, 17 June 2009), data being collected during 2007, the majority ranked their level of optimism as neutral (44%). It may be that participation in a trial is an influential factor in increasing optimism about the effectiveness of the gene therapy product, since there is still optimism in Blair *et al.* (1998)'s sample when the product was much less developed than to date.

The researcher did not ask participants in the current study whether they had any concerns regarding the gene therapy product. In the Blair *et al.* (1998, p.220) study, twelve patients did not report being adversely affected by participation in the single dose gene therapy trial and "almost all" believed themselves to have been at no risk from the product. For the six participants in the current study who had seen no change in expectation, only two referred to waiting until the gene therapy product worked before they could trust in it as a product. There was no mention that the product might not be developed safely.

Hoping gene therapy treatment works for others in the future

It is useful to consider the sub-theme “Hoping gene therapy treatment works for others in the future” at this point because of its clear link to how participants manage both hope and expectation about gene therapy.

There was overlap between hoping for benefit for oneself in the future and hoping for the eventual benefit of others. Six participants expressed the hope of a future cure for CF and six believed gene therapy to potentially be a partial cure or an improved treatment. This differed from a study by Thomas *et al.* (2007) who found that adults with CF did not seem to believe that gene therapy would be a potential cure. It may be the case that participants’ involvement in the Run-in study had an impact on these beliefs.

Of the twelve participants, there were six who expected that future gene therapy treatment would make a “huge difference” for those with CF, anticipating that future generations would not have to suffer the life-limiting effects of CF and that less medication would be required to manage the condition. Of these participants, four explicitly based their reasoning upon empirical knowledge, albeit not in any depth. This finding contrasted with the Blair *et al.* (1998, p.219) study where fifteen out of twenty patients gave a positive estimate that gene therapy would effectively treat CF in the future. Instead of basing this on critical evaluation of evidence, fourteen of these participants based this on “gut feeling.”

In the current study, participants expected that gene therapy would have the greatest benefit for children before the development of lung damage. This is similar to findings

in Blair *et al.* (1998) where babies and young children were anticipated to benefit the most from treatment before the development of permanent lung damage. In the findings by Duff (A. Duff, personal communication, 17 June 2009), the majority of participants (83.7%) believed that those currently aged five and under and future generations would be the beneficiaries of gene therapy.

One explanation for participants in the current study concurrently demonstrating altruism and expectation of personal benefit is that there was participant perception of researchers looking for clinical benefit from the multi-dose gene therapy trial. This is compared to there having been no such expectations within the earlier single dose trial (Blair *et al.*, 1998). Nevertheless, when participants in Blair *et al.*'s (1998) study were asked whether they expected to benefit personally from gene therapy in the future, five expected fewer chest infections and reduced medication, five expected disease stability and three hoped for improvement in their lungs. Participants were therefore expressing an expectation of gene therapy that was similar to participants' expectations of personal benefit from the gene therapy trial in the current study.

In the current study, one participant's concern about being well enough to receive gene therapy treatment in the future finds resonance with the findings from Duff where almost one third (31.14%) of all 266 respondents thought that it would be those whose health was "well above average" that would benefit compared to 20.18% who believed that it would be beneficial for those of "poor health."

It is therefore clear that unlike the above studies, participants in the current study did find that both their expectations and hopes about gene therapy were raised. This seems

to be linked to actually participating in a trial that will potentially lead to a gene therapy trial as well as their experience of visiting Southampton where they had contact with new technology which made the trial seem much more ‘real’ to several participants.

Participants therefore did have expectations and hopes of participating in the gene therapy trial and of obtaining some clinical benefit from it, as well as hope in the gene therapy product in the future. As has been discussed, they have managed these expectations by not thinking too far ahead and not raising their hopes too high. Participants also found the ongoing trusting relationships they had with the research team, their local CF teams and the CF Trust as very useful coping strategies to manage these hopes and expectations.

Trusting the research team and the information they provide

Participants in the current study expressed a general sense of trust in the research team, including trust in their selection procedures for the gene therapy trial and in their ability to deal well with participants’ enquiries. Trust was also strengthened through other perceived clinical benefits obtained from being on the Run-in study. Wendler *et al.* (2003) indicate that participants generally trust research teams. There is evidence that patients invest trust in the professionals running clinical trials even before meeting them (Jenkins & Fallowfield, 2000). There is also evidence of patient trust in doctors involved in clinical trials and this has been given as a frequent and stable reason for participation in cancer trials (Penman *et al.*, 1984).

Although two participants in the current study referred to being a “guinea pig,” the researcher understood use of this word in a light hearted way meaning the undertaking

of study visits and test requirements as directed. There was no indication that participants had lost trust in how the research team was using their contribution to the trial. This is in contrast to situations where patients are treated inappropriately by clinical research teams as merely objects i.e. as something to be acted on (Jonas, 1969)

Of the twelve participants in the current study, ten had not asked the research team for any extra information to the initial information they had been provided with, although three of these expressed confidence that the team would be able to deal well with their enquiries. This was the same finding in Blair *et al.* (1998) where three participants felt that they would be able to ask for more information if desired. Some studies have shown that clinical research teams may take advantage of their participants' lack of understanding of research procedures (Wendler *et al.*, 2003). However, there was no evidence of this in the current study, and participants did not appear to feel the need to fully understand gene therapy as a pre-requisite of participation. It may well be that, for participants, managing the amount of information they had about gene therapy was a way of managing their expectations about gene therapy. However, they were very comfortable with asking the research team, their local CF team or the CF Trust if they had any need to find out further information.

There was evidence of participants believing information from the medical research fellows in the research team because of their privileged position regarding knowledge. This corresponds to the suggestion by Lidz & Appelbaum (2002) that participants in clinical trials bring prior expectations of the doctor-patient relationship to participation in the trial. However, one of the participants in the current study did indicate a level of frustration in trying to ascertain the research outcomes of the trial. Whilst there was not

sufficient evidence to say that this was a clear case of research goals differing between participant and researcher (Lidz & Appelbaum, 2002), it is more likely that the expectations of the participant exceeded those of the researchers. The participant recognised that there was uncertainty regarding the outcome of the trial yet appeared unsatisfied due to information not being “freely given” to help with his own uncertainty. This raised the question of how both participants and research teams manage uncertainty in the development of novel therapies and how participants are helped to manage their hopes and expectations.

Trusting local CF teams and the CF Trust

In the current study, five out of twelve participants showed evidence of trust in their local CF teams during their participation in the Run-in study, indicating that whilst they would look for information about gene therapy from the research team, they would also discuss aspects of the trial with their local CF teams. This finds support in the findings by Thomas *et al.* (2007) with most respondents wishing to discuss gene therapy further with their local CF teams, although the largest source of information for two-thirds of the respondents was the UK CF Trust (Thomas *et al.*, 2007).

Moos and Holahan (2007) have identified that people with chronic illness have to undertake the adaptive task of forming relationships with health care providers. This is evidenced in patients with CF who often have ongoing relationships with their local CF team. It is therefore an interesting finding that participants felt they benefited from the support of their local CF teams as they participated in the Run-in study.

Further, in Duff's findings (A. Duff, personal communication, 17 June 2009), respondents indicated that they would like more information about gene therapy routinely given to them by their local CF teams and that they wanted this information to be clear and realistic i.e. not giving false hope after having waited so long for gene therapy. Closer liaison therefore between the research team and the local CF teams could be useful, especially at key stages of the research process.

Half of the participants in the current study trusted the information from the CF Trust regarding the gene therapy trial and would continue to trust the CF Trust as a reliable source of future information. This is similar to the findings by Duff (A. Duff, personal communication, 17 June 2009) where 58.9% of respondents cited the CF Trust as one of the most common trusted sources of information for participants. However, 69.2% of the respondents overall considered the CF local team to be the most important source of information about gene therapy (A. Duff, personal communication, 17 June 2009).

Late diagnosis

The findings of the current study indicate that participant experience of the Run-in study was influenced to some extent by time of diagnosis. Little has been known about the specific needs of those diagnosed with CF as adults (Widerman, 2003). However, there is evidence to suggest that there are different stages of adjusting to diagnosis made in adulthood, one of which is that of male patients coming to terms with infertility. This issue emerged in two males who had been diagnosed late, although one said that it was "water under the bridge" (*Participant 2, line 124*), having come to terms with infertility and with his diagnosis. However, the other male participant was still coming to terms with his much more recent diagnosis. Widerman (2003) recognises

that local CF teams should assess the needs of those with late diagnosis and help patients to address these needs. It may be that patients who participate in the trial with a relatively recent diagnosis have their hopes or indeed expectations of a cure influenced by the process of continuing adjustment to diagnosis.

Indeed, the two most recently diagnosed participants, both of whom were diagnosed within the last five years, were more hopeful of personal benefit from the trial than those who had received an earlier diagnosis as an adult. They also appeared to be more anxious that the trial succeed, one of these being the participant who became upset about the possibility of not being able to participate in the gene therapy trial. However, it may also be the case that participants with late diagnosis perceive that they are too well to receive physical benefits from the trial, with the two remaining participants with late diagnosis indicating this in their responses.

It has become clear to the researcher that people with CF who would potentially participate in gene therapy trials could include different groupings of patients e.g. those who have had a late diagnosis, those whose CF is seen as mild, those who are in the moderate category whose realistic chance of benefiting from gene therapy may be restricted, and those who are children. Jaffe *et al.* (2006) highlight the complex family dynamics at work in including children in clinical research. The differing needs and vulnerabilities of these various groups should be considered when offering support to those participating in gene therapy trials in the future.

4.2 Summary

The main aims of the study were to discover the expectations that participants recruited for the CF Run-in study had of the gene therapy trial and of gene therapy in general and to ascertain whether these expectations changed during their participation in the CF Run-in study. This included whether participants had any misconceptions of gene therapy. Difficulties and benefits of participation in the Run-in study were also explored.

Eleven out of twelve participants explicitly expressed the hope of being selected to participate in the gene therapy trial. The researcher found that ten of the twelve participants hoped that the gene therapy trial would have some clinical benefit for them. Four of these participants said that they did not have any expectations or did not know what to expect. The remaining two participants said that they did not expect personal benefit but still expressed hope that the trial would work for those known to them or those in the future.

Half of the participants expressed the hope of a future cure for CF delivered by gene therapy and six participants hoped that gene therapy would potentially be a partial cure or an improved treatment. Six participants had an increased expectation of gene therapy being an effective treatment in the future. It was anticipated that gene therapy would have the greatest benefit for children and young people before the development of lung damage.

Six participants' hopes of getting clinical benefit from the gene therapy trial were unlikely to be met e.g. experiencing stable lung function, living a normal life or having

CF removed altogether. There was therefore some unrealistic optimism in half the participants on the current study. However other patients participated with apparently realistic expectations. Participants utilised coping strategies such as not thinking too far ahead, and not raising their hopes too much, as well as relying on the research team, their local CF team and the CF Trust to help manage these expectations.

Time of diagnosis may also have had an effect upon participants' experience of the trial and whether or not they experienced psychological difficulties or physical benefits. This underscores the need for attention to be paid to the different groupings of patients who may be participating in the gene therapy trial so that adequate support is put in place. Most participants found participation in the Run-in study a positive experience and four had experienced clinical benefits from participation.

Altruism was a motivating factor for seven participants in the current study and it seems likely that some patients would have participated even if there were no prospect for personal direct benefit from gene therapy. There was evidence of six participants who had seen an increased expectation of gene therapy being an effective treatment in the future.

4.3 Reflections on the Research Process

4.3.1 Participants' Perceptions of Being Interviewed

As outlined above (Section 2.6.2: Interview Procedure) eleven out of twelve participants were asked about how they had found the experience of being interviewed. No participant commented on how they had found the experience of being interviewed. Five participants commented that the interview process was "fine," "okay" or "all

right.” In addition, two of the twelve participants said that they had not known what to expect and two explained that they had found it hard to express their thoughts in words. Whilst one found the interview how he had imagined, another found it different to what he expected i.e. something “more, I don’t know, conversational” (*Participant 2, lines 432-433*). One participant thought the researcher would be asking questions about CF and his own health behaviour. The remaining participant found that the interview process had helped him to reflect on his participation in the Run-in study:

You know it’s not very long, it’s only what half an hour but you’ve still just that little bit time to sit down and talk to somebody else about it and just think maybe what you actually feel about the whole thing a little bit more in-depth. (Participant 12, lines 894-899)

None of the participants expressed negative thoughts or feelings about being interviewed. Prior to interview, one of the participants who found it difficult to express himself verbally had alerted the researcher to this fact but he indicated that he still wanted to help the study.

4.4 Researcher’s Reflections on the Interview Process

The researcher was aware of the role that her own values, interests and presuppositions could play in directing the course of the interview. For example, the researcher was interested in one participant’s experience of teacher training because she herself had trained as a teacher. Whilst discussion of a topic of mutual interest was helpful for building rapport, the length of discussion was slightly long. This was an example of possible bias though it was likely to be benign in terms of the research aims.

The researcher recognised that during the process of interviewing twelve participants, she experienced a growing sense of hope about the possibility of an effective gene

therapy treatment for CF. However, the researcher tried not to use language that reflected this sense of hope although she was aware that tone of voice or facial expression might have indicated a shared sense of hope with the participant being interviewed, especially in the latter stages of the study. The researcher was also aware of the investment of the research team in the gene therapy product and recognised that she did not want to disappoint them with findings that did not fit with their own hopes of gene therapy being developed. This emerged more clearly during the researcher's analysis in her memo writing; it also emerged in discussion with her academic supervisor which helped to make implicit bias more explicit.

The researcher reflected on the need to balance an interview in terms of building rapport, being responsive to the interviewee's interests and leading the interview. The researcher recorded in her methodology diary that she used follow-up questions to encourage participants to explain their definition of words or expressions e.g. "having a normal life." This was because the researcher wished to avoid using her own assumptions in interpreting expressions participants used, albeit she acknowledged her role in the interpretive understanding of the data.

The researcher also tried to help participants to relax prior to interview as she was setting up the digital voice recorder. The researcher used this time to begin to gauge how best to minimise any inequalities that would be detrimental to the interview process e.g. to reduce any effects of an age difference between researcher and participant. The appropriate interview approach for each participant was chosen, based on the researcher's previous teaching and clinical experience and thus encouraging the participants to be research collaborators. The researcher worked with participants to

maximise the opportunity for them to respond to questions. For example, when participants found that it was difficult to explain something, the researcher helped the participant to approach the issue from a different angle e.g. “If your family or friends asked you what you know about gene therapy, how would you explain it to them?”

The researcher evaluated her interview technique after each interview to assess her influence upon the interview process e.g. whether she asked any leading questions or whether there was an appropriate balance between listening and speaking. As a result the researcher developed her interview techniques over the course of the current study, resulting in decreased speaking time and increased listening time for the researcher. Participants were asked how they had found the interview experience and these responses were recorded from interview three onwards, the researcher having realised the benefit of a verbatim record of the participant’s evaluation of the interview. This was with the aim of encouraging participants as research collaborators. As the last interview was brought to a premature close, this reflective process was not able to be undertaken (See Section 2.6.2: Interview Procedure).

4.5 Methodological Considerations

The researcher recognises that there were methodological limitations and strengths in the study. Interpretation of the findings has been undertaken with this awareness.

4.5.1 Limitations

The methodological limitations identified are as follows: the researcher having limited experience of qualitative research, respondent validation and selection bias.

4.5.1.1 Researcher's Limited Experience of Qualitative Research

The researcher acknowledges that limited experience of qualitative research has had an influence upon how the current study has been undertaken. The researcher scheduled the first few interviews within a relatively short time frame, although this was also due to arranging interviews at the convenience of the participants. Further, the time taken for the current study to go before an ethics panel was prolonged due to significant consideration of whether it should be a substantial amendment to the Run-in study or a separate study. The latter was eventually decided after discussion with both the Edinburgh and London research sites.

It was likely that the earlier interviews conducted were limited by the researcher's inexperience in not asking sufficient follow-up questions to generate rich data from the participants. However, the researcher developed additional questions to saturate emerging themes and she acknowledges that pure data saturation may not have been achieved (See Section 2.1.4: Process of Grounded Theory).

Whilst the researcher aimed to follow a Grounded Theory approach, she acknowledges that she did not follow axial coding as outlined by Strauss and Corbin (1998). Further, the interview schedule was not sufficiently flexible to follow through on areas of interest raised within the interviews such that these were not explored as thoroughly as they would have been within a traditional Grounded Theory approach e.g. examining the difference between hope and expect in more depth and developing these findings as a potential category or concept. In addition, the semi-structured nature of the interview schedule was more characteristic of an Interpretative Phenomenological Analysis (IPA) approach to exploring and gathering data (e.g. Smith & Osborn, 2003).

All interviews were recorded accurately, except for one in which the digital voice recorder's file reached capacity and the last three minutes approximately were not recorded. On realising this immediately following the interview, the researcher recorded by hand what had been said with the recognition that this was not exactly verbatim in the manner of a digital recording.

4.5.1.2 Limited Respondent Validation: Preliminary Findings

Although the use of respondent validation is an undoubted strength in qualitative methodology and the researcher had sent out preliminary findings for participants' comments, only one participant commented on these findings. His comments were that participants had given "neutral statements regarding expectations":

Clearly nobody wants to be seen to step out of line with how they 'think' you'd like them to respond. In other words everyone has to be drawn to the middle. As for myself, I remain very positive that gene therapy might well be my meal ticket. If I receive gene therapy, I expect something to happen, assuming something happens, I expect it to be for the best, therefore: gene therapy will positively affect me...

It is acknowledged that the intention and process of respondent validation was a potential strength methodologically. The researcher felt that because of the small number of responses this could be a potential limitation. However, following dissemination of the full findings, seven participants gave comment on the findings (See Section 4.5.2.5: Respondent Validation: Final Findings)

4.5.1.3 Selection Bias

Participants on the current study had been invited to participate in the CF Run-in study because of the main criteria that they had mild to moderate disease severity. Thus those with more severe disease were inherently excluded from the study. In discussion with

the research manager for the Run-in study, it was ascertained that the twelve participants were representative of the Run-in sample as a whole in terms of disease severity, age, gender and geographical location.

Of the forty-two participants on the Run-in study, twelve chose to be interviewed for the current study. It may be that these self-selecting participants were more willing or were more available to discuss their expectations of gene therapy and what it was like to be a participant in the Run-in study. This could have limited the researcher's access to other perspectives on expectations, the level of support other participants might have required, or experiences of participation e.g. those who had doubts about continuing participation in the Run-in study.

4.5.2 Strengths

Although there were limitations, the researcher posits that the current study also displayed significant strengths. These will be considered in the following order: clear communication with the research team, qualitative methodology, ethical rigour, theoretical sampling, effective supervision and reflection.

4.5.2.1 Communication with the Research Team

The researcher maintained good communication with the research team throughout the study. The researcher gave a presentation on her proposed study prior to undertaking interviews. She kept up-to-date with the progress of the Run-in study and discussed aspects of this with the research team, who were also informed of the findings of the study.

Whilst there were limitations in terms of possible bias and the researcher's initial sense of constraint on producing results which she perceived as contrary to the interests of the team, the researcher worked to minimise these limitations. The researcher found that the strengths of being involved with the research team were greater than managing possible bias e.g. gaining information on the progress of the study and having queries answered regarding the nature of gene therapy for CF.

4.5.2.2 Qualitative Methodology

The use of qualitative methodology in the current study enabled participants to openly discuss their experiences on the trial and their expectations of the gene therapy trial and of gene therapy in general. This gave insight into their expectations, how these were being managed and into why expectations had changed or remained stable. It also identified areas where benefits and/or difficulties were experienced through participation in the Run-in study.

4.5.2.3 Ethical Rigour

The researcher contends that the current study was undertaken professionally and with due consideration of the participants' best interests, as outlined in 2.3 of the Method. The researcher monitored participants' responses to ensure their well-being. Participants were aware that support was available should this have been required.

4.5.2.4 Theoretical Sampling

As a method-based qualitative approach, grounded theory uses theoretical sampling after coding and analysis to identify gaps in the developing theory. Based on this, the researcher identifies the data that needs to be collected in order to supply this

information and then develop and refine theory (See Section 2.1.4: Process of Grounded Theory). In theoretical sampling, research participants or research topics are strategically selected to fill the gaps identified. In the current study, there was a limited available pool of potential participants such that it was not possible to fully select participants purposefully. For example, the researcher's sample was representative of the age group within the Run-in study but the researcher would have liked to have recruited more participants with late diagnosis for theoretical sampling.

Nevertheless, the researcher was able to develop questions for subsequent interviews in order to explore as much as possible the full range of response within the subject area. The researcher acknowledges that earlier detail may have lead to a more developed initial framework yet later data was rich and still allowed for the development of categories and subcategories.

4.5.2.5 Respondent Validation: Final Findings

There were seven participants who expressed several opinions on the final findings. Three participants found the current study to be interesting. There were three who commented that the findings were as expected, with one making the additional comment that the results were balanced. Three participants believed that the expectations of the gene therapy trials expressed in the current study were largely similar. One participant believed that it would be interesting to compare the views of the researchers and the participants. Two participants found the study provided a good opportunity to think about aspects of the trial. Another commented on having a sense of ownership in the gene therapy trials. A further comment from one participant was that it was a "shame" that the research was behind schedule.

4.5.2.6 Effective Supervision

Meeting regularly with both the researcher's academic and clinical supervisor respectively ensured that the researcher's qualitative skills developed effectively and that issues arising from the interview process were explored thoroughly. The researcher benefited from the support of both supervisors. Following initial independent coding by both supervisors, the joint meetings in which coding and themes were discussed were very useful in clarifying important data and processes. The experience of both supervisors added to the quality of the research. One was a chartered health psychologist with qualitative research experience in the health field and the other a chartered clinical psychologist with substantial experience in CF.

4.5.2.7 Researcher's Reflection

The researcher used separate reflection and methodology diaries to keep notes of reflections on the researcher's own practice, observations of participants during interviews, and of amendments made e.g. adding questions to the interview schedule. The researcher was aware of being in a privileged position by being allowed into the participants' world. The researcher was also very aware of not having CF and maintained a respectful attitude throughout the interview process.

Experience of working as a trainee clinical psychologist with patients with CF informed the researcher's approach to the interviews and helped her to have a context in which to make sense of the participants' responses. This would have been very difficult without knowledge of the progressive nature of CF and of the treatment required, and of how patients with CF vary in managing their condition.

The researcher was also aware of the different stages of CF. For example, she became conscious of three participants in young adulthood being dependent upon parental support, this often being a protracted period of transition to independent adulthood. The researcher was helped to analyse the material from all the interviews by considering the different life cycle stage of each participant.

However, she did not wish to assume how a participant was experiencing CF and indeed how this would influence their expectations of gene therapy and participation in the trial. The researcher was mindful of always encouraging the participants to tell their own stories. Nevertheless she acknowledges that previous knowledge of CF may have unconsciously influenced how she perceived the participants.

Being a trainee clinical psychologist also helped the researcher to manage the sometimes intense emotions expressed. The researcher believed that her clinical psychology training greatly helped her in dealing with moving accounts, ethical issues and significant silences. Further, it helped her to ask questions sensitively.

The researcher's experience of individual work as a teacher helped her to engage participants quickly and at a level that was appropriate to them e.g. showing interest in their responses and taking their comments seriously. Teaching experience also helped her to use a different interviewing style from that used in therapy. On the three occasions when interviews began to move towards a therapeutic mode, the researcher was able to handle the tensions between monitoring participant well-being and not interviewing as a therapist.

In discussing gene therapy with colleagues within a local CF team, the researcher realised the variety of perspectives and knowledge regarding the likely effectiveness of gene therapy for CF. This helped her to reflect on the impact that such a new and developing field has upon the professionals who may be called upon to answer questions when the outcomes are not yet known. The researcher reflected that her role was to remain neutral when participants' were describing expectations of gene therapy treatment. This was in order to elicit their accounts openly and without bias.

The researcher also reflected upon her own level of knowledge of gene therapy and how this might have affected the current research. In interviewing participants the researcher was struck by the occasions when they assumed greater knowledge of gene therapy on the part of the researcher than was actually the case. Whilst the researcher helped participants to understand her limited knowledge, she did at these times wonder how far participants perceived her as being separate from the Run-in study. However, whilst she did not perceive that participants were answering questions to influence positive selection for the gene therapy trial, she acknowledges that this might have been an implicit process.

4.6 Contributions of this Study

The researcher posits that the current study contributes to existing research in the five following ways:

1. Discovering that participation in a Run-in study alone is sufficient for some participants to develop increased expectations of gene therapy treatment i.e. clinical benefits for themselves and for future generations;

2. Discovering that there is evidence of unrealistic optimism regarding the level of likely personal benefit from gene therapy treatment e.g. having all CF symptoms removed;
3. Discovering however, that participants use a variety of strategies to manage their expectations of gene therapy e.g. not raising their hopes and not thinking too far ahead;
4. Discovering that participants may require support if they are not selected for the gene therapy trial or for when the trial comes to an end;
5. Discovering that there may be a difference in how participants experience the trial dependent upon time of diagnosis and adjustment to this; and
6. Discovering that participants are relying on the support of their local CF teams during the Run-in process.

4.6.1 Clinical Implications

Based on the above findings, and in consultation with the researcher's clinical supervisor, the following recommendations are made:

1. A standard clinical interview should be offered for all those not accepted for gene therapy trial;
2. A standard clinical interview should be offered at the trial's conclusion;
3. Screening for anxiety pre-, during and post-participation should be undertaken. This could mean adding in a validated screening tool such as the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) with the Quality of Life measurement already given to participants at key stages of the research process;

3. Screening for participants with late diagnosis should be done to identify those who are still in the process of adjusting and may find participation more difficult. This may also include identifying other participants who may need more focused support; and
4. Continued good communication between local CF teams and the research team, with information continuing to be provided between teams.

4.6.2 Future Research

The findings of the current study indicated areas for future research. Due to the finding that there was increased expectation of gene therapy treatment in half of the participants on the Run-in study, extended study into the expectations of participants on the gene therapy trial would explore factors that influence expectations and how these are managed e.g. whether expectations increase with the 50% possibility of receiving active treatment.

Due to the emergence of some specific findings dependent upon late diagnosis, it became clear that participants in gene therapy trials could potentially be grouped e.g. those who have had a late diagnosis, those whose CF is seen as mild, those who are in the moderate category whose realistic chance of benefiting from gene therapy may be restricted, and those who are children. The differing needs and vulnerabilities of these groups should be considered when offering support to those participating in gene therapy trials in the future.

4.7 Conclusion

Greater optimism was noted by participants in the current study about the potential of gene therapy, compared to that found by Blair *et al.* (1998) and Duff (personal communication, 17 June 2009). Some of the positive expectations are unlikely to be met by the gene therapy trial but there was also evidence of apparently realistic expectations. Participants managed expectations by utilising individual coping strategies as well as through ongoing trust in the research and local CF teams. There was evidence of expectations of gene therapy increasing as a result of participation in the Run-in study. Most participants were realistic that true benefit from CF gene therapy may ultimately be for future generations.

In general participants found being in the Run-in study a positive experience, although those with late diagnosis could be a group who may need support in managing their expectations about participation in gene therapy trials. Further research is needed with this group in terms of whether they have adjusted to diagnosis sufficient to facilitate participation in gene therapy trials. Consideration could also be given to other groups who participate in gene therapy trials who may benefit from support e.g. participating children and their parents.

A recommendation is made for further support and a clinical debrief interview to be given to participants on this trial and future gene therapy trials especially at key points e.g. if they are not selected, or when the trial comes to an end. The recommendation is made that a validated measure for screening mood such as the HADS be added in to the existing Quality of Life measure participants are completing as part of the Run-in study

which will assist in identifying low mood or anxiety and enabling appropriate support to be put in place.

The researcher acknowledges that given the small sample size of participants, further study is needed to corroborate and extend these findings.

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APPENDICES

APPENDIX 1	Demographics Sheet
APPENDIX 2	Interview Schedule
APPENDIX 3	Patient Information Sheet
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